Post-Neonatal Tetanus : Issues in Intensive Care Management

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Abstract. Tetanus is an acute neurological disease characterized by muscle rigidity and spasms, autonomic dysfunction and in severe forms requires respiratory and hemodynamic support. Though it is entirely preventable by immunization, it still occurs in developing countries causing significant morbidity and mortality. Intensive care management of tetanus is fraught with problems of ventilator-associated pneumonia, nosocomial sepsis and a variety of other complications. Various treatment protocols have been tried in managing diverse manifestations of severe tetanus but the consensus is yet to emerge. In this review we have discussed the pathophysiology, clinical features and management controversies and suggest on basis of our experience use of high dose diazepam (20 - 120 mg/kg/day) and vecuronium with mechanical ventilation if required for control of spasms, and early detection of autonomic dysfunction and use of propranolol, in our circumstances. [Indian J Pediatr 2001; 68 (3) : 267-272]

Key words: Post-neonatal tetanus; Intensive care treatment; Diazepam therapy; Autonomic instability

Tetanus was first described in Egypt over 3000 years ago. It is unfortunate that despite availability of active and passive immunization, tetanus remains a major health problem in the developing world.¹ There are about 8 lakh to one million deaths due to tetanus worldwide.¹ Eighty percent of these deaths occur in Africa and South East Asia.²

Tetanus in its early stages, when it is most amenable to treatment, is often unrecognized and severe fatal cases are under reported.³ The clinical course of tetanus is often unpredictable and patients should be closely monitored.⁴ The facilities available to manage severe tetanus have major impact on the therapeutic options and mortality.⁴ Availability of artificial ventilation should prevent most of the early deaths caused by acute respiratory failure and uncontrolled spasms, but autonomic disturbances that appear subsequently during course of the illness along with intensive care related complications (ventilator-associated pneumonia, gastrointestinal hemorrhage) then become the major cause of death.^{5,6} The aim of this review is to describe the pathophysiology, areas of controversy in the management of tetanus and to outline the principles of intensive care management for severe tetanus with a reference to the practical experience at Chandigarh.

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Pathophysiology

Tetanus is caused by *Clostridium tetani*, an anaerobic gram-positive bacillus. After colonizing the wound, if the local tissue oxygen content is low, the spores transform into vegetative forms and proliferate. Factors facilitating subsequent development of tetanus include the presence of foreign bodies, necrotic tissue and suppuration in the local wound. The vegetative forms produce the toxins, tetanospasmin and tetanolysin. Tetanolysin damages the viable tissue and lowers the redox potential in the wound further. Tetanospasmin causes the clinical manifestations of tetanus.

Tetanospasmin enters the nervous system at the neuromuscular junction of the alpha motor neurons.⁷ Toxin is then carried by retrograde axonal transport to the cell body. Toxin migrates trans-synaptically to other neurons, the most important being presynaptic inhibitory neurons, preventing neurotransmitter release. The neurons most commonly affected are the spinal inhibitory neurons and parts of the sympathetic nervous system. The consequent loss of inhibition results in the clinical manifestations of the disease. Once tetanospasmin has bound to its receptor at the neuronal cell body, the inhibition of neurotransmitter release is permanent and recovery depends upon formation of new synapse. There is blood-borne spread of toxin from the site of entry to the brain at the area postrema of the floor of the fourth ventricle where the

blood brain barrier is non-existent. This may explain the early manifestations of tetanus like trismus and nuchal rigidity.

Autonomic Dysfunction

The hallmark of sympathetic over activity are fluctuating heart rate and hypertension, sometimes followed by hypotension, cardiac arrhythmias, peripheral pallor, sweating and pyrexia. Proposed mechanisms for autonomic dysfunction include the effect of the toxin on brainstem and autonomic interneurons, a direct effect of the toxin on the myocardium and because of adrenal inhibition.⁸ Fluctuations in blood pressure and heart rate appear to be related to changes in systemic vascular resistance rather than cardiac output or left ventricular filling pressure. Sympathetic overactivity predominates but parasympathetic involvement does occur: sudden cardiac arrest is a complication of severe tetanus as also bradycardia, excessive salivation and increased bronchial secretions.

DIAGNOSIS

The diagnosis of tetanus is entirely clinical (Table 1).⁹ It typically follows deep penetrating wounds where anaerobic bacterial growth is facilitated. The most common portals of infection are wounds on the lower limbs, non-sterile intramuscular injections and

TABLE 1. Clinical Criteria for Diagnosis of Tetanus⁹

1. An illness characterized by the acute onset of hypertonia and/or painful muscle contractions (usually of the jaw and neck) and generalized muscle spasms without other apparent causes such as drug reactions, other central nervous system disorders, hysteria.
2. No history of contact with strychnine.
3. Subsequent disease course consistent with tetanus.

compound fractures. However, in up to 30% of patients no portal of entry is apparent.¹⁰ It can follow from chronic infection such as otitis media or a decubitus ulcer. Tetanus acquired after intramuscular injection with quinine is associated with a higher mortality than other modes of acquisition.¹¹ The site of origin has no prognostic significance except for tetanus of uterine origin which is associated with poor prognosis.

The incubation period may vary from 24 hours to many months. The period of onset is defined as the time interval between the first symptoms and the occurrence of spasms and varies from 48 hours to

several days. Trismus (lock-jaw) due to rigidity of the masseters is the often the first symptom. Sometimes, tetanus can be localized at the site of injury causing local rigidity and pain. Generalized tetanus is the more common form of the disease. It presents with rigidity, opisthotonus and spasms. Spasms are painful and if prolonged, may lead to rhabdomyolysis and its complications, laryngeal obstruction, acute respiratory failure and arrest. Spasms are more prominent in the first two weeks. Autonomic disturbances usually occur some days after the spasms and reach the peak during second week of the disease. Rigidity may last beyond the occurrence of spasms and autonomic disturbances. Severity of tetanus can be graded on basis of Ablett's criteria (Table 2).¹² The criteria may be helpful in deciding on patients who might require intensive care monitoring specially in developing countries where such facilities are limited.

TABLE 2. Ablett's Criteria for Classification of Severity of Tetanus¹²

Grade I	Mild or no respiratory involvement and dysphagia
Grade II	Moderate respiratory involvement and Trismus
Grade IIIA	Severe respiratory involvement, generalized rigidity and major spasms, no autonomic involvement
Grade IIIB	Severe manifestations as above with autonomic dysfunction

A retrospective analysis of our patients admitted in pediatric intensive care unit between 1996 and 2000 revealed otogenic tetanus as the commonest form of tetanus, with head and neck being the commonest portal of entry (Table 3).

Principles of Management

The care of a patient with tetanus should aim to satisfy five goals:

1. Neutralization of the unbound toxin
2. Eradication of the source of toxin
3. Control of rigidity and muscle spasms
4. Control of autonomic dysfunction
5. Supportive care

1. Neutralization of the Unbound Toxin

Passive immunization shortens the course and may reduce the severity of tetanus.¹³ The human tetanus anti-serum is the preparation of choice, prepared from plasma of healthy human donors immunized with tetanus toxoid. The half-life of the human tetanus anti-serum is 24.5 - 31.5 days. The equine form of the toxin has a higher incidence of anaphylactic reactions and

TABLE 3. Characteristic of Patients with Severe Tetanus (n=15)
(Treated over 4 years in PICU, PGIMER 1997-2000)

Male : Female	8:7
Age ≤ 6 years	9 (60%)
Age ≥ 6 years	6 (40%)
Immunization	
• Complete (first 3 doses + 2 boosters)	0
• Primary (first 3 doses only)	7 (46.66%)
• Unimmunized	8 (53.33%)
Mode of injury	
• Otogenic	9 (60%)
• Post-traumatic	5 (33.33%)
• Unknown	1 (6.66%)
Entry site	
• Otogenic	9 (60%)
• Lower limb	4 (26.66%)
• Upper limb	1 (6.66%)
• Unknown	1 (6.66%)
Incubation period	2- 10 days (mean - 5 days)
Period of onset	48-192 hours (mean - 62 hours)
Symptoms at admission	
• Lock jaw	14 (93.33%)
• Spasms	9 (60%)
• Fever	7 (46.66%)
• Rigidity	5 (33.33%)
Mortality	5 (33.33%)

short half-life (2 days), but is less expensive. If available, human tetanus anti-serum is the preparation of choice. In established cases patient should receive 500 to 1000 IU/kg of equine anti-toxin either intravenously or intramuscularly. If available, human tetanus antiserum can be administered intramuscularly at a dose of 5000 to 8000 IU. Although antisera will have effect only on the unbound toxin (present in serum samples of only 10% of cases) it should be administered in all cases irrespective of the duration or severity of the disease. Whether it should also be infiltrated locally at the portal of entry is unclear and should be examined prospectively. For prophylaxis 1500 - 3000 IU equine or 250 - 500 IU human anti-tetanus immunoglobulin should be given.¹⁴ Passive immunization should be instituted as soon as possible after the injury. There is no role for intrathecal administration of anti-toxin.¹⁵

Removal of the Source of Toxin

The source of toxin is treated by excellent wound debridement and administration of intravenous

antibiotics. Some authors advocate extensive wound debridement while others maintain that it is not essential because it has no effect on the course of the disease once tetanus has developed.^{16, 17, 18} Overall, wound debridement appears to be helpful. Wound debridement at admission was done in all our cases, if required.

Penicillin remains the antibiotic of choice in tetanus. The dose is 1 lakh units/kg/day intravenously or intramuscularly for 7 to 10 days. The structure of penicillin is similar to γ -amino butyric acid (GABA), the principal inhibitory neurotransmitter in the central nervous system. Penicillin therefore acts as a competitive antagonist to GABA. In high cumulative doses it can thus cause CNS hyper-excitability. Metronidazole is a safe alternative as reduction in mortality and requirement of fewer muscle relaxants and sedatives has been reported with its use.¹⁹ The role of pyridoxine²⁰ and corticosteroids²¹ in tetanus is controversial. Currently steroids are not recommended in the management of tetanus. Ten of our patients received crystalline penicillin while five received metronidazole. There was no difference in mortality between the two groups. None of our patients were given steroids or pyridoxine.

3. Control of Rigidity and Spasms

No single drug or group of drugs has been consistently effective in controlling rigidity and spasms in severe tetanus. Benzodiazepines are the commonly used agents for the control of rigidity and spasms. Diazepam has a wide margin of safety, has a rapid onset of action, can be given orally, rectally or intravenously. It is a sedative, anticonvulsant and a muscle relaxant and has a long cumulative half-life of 72 hours. The exact dosage of diazepam used in post neonatal tetanus have varied from 3 mg to 20 mg/kg/day.^{22, 23} It is said that high dose diazepam causes myocardial and respiratory suppression. Establishing a correct therapeutic window is extremely difficult. Midazolam is an alternative, but is expensive and not freely available in regions where tetanus is seen frequently.²⁴ Phenothiazines like chlorpromazine have been widely used in tetanus. Its complex pharmacological actions include partial blockage of α -receptors, suppression of brain stem reticular formation and anti-cholinergic effect.²⁵ Morphine may be used as a sedative without compromising cardiac performance.^{25, 26}

In our patients we used intravenous diazepam infusion as the initial sedative agent and muscle relaxant. The initial dose was 20 mg/kg/day that was increased in increments of 5 mg/kg till control of spasms or

appearance of side effects. The average dose used in our patients was 55.4 mg/kg/day (range: 20 - 120 mg/kg/day). One patient developed poor respiratory effort on 120 mg/kg/day of diazepam infusion and required mechanical ventilation, two patients had hypotension requiring fluid boluses. Diazepam by enteral route may be used once spasms are well controlled. There is no consensus on maximum enteral dose of diazepam, but we have used up to 60 mg/kg/day in 4 - 6 divided doses through naso-gastric tube without serious side effects as respiratory failure and/or myocardial depression.

Long acting muscle relaxants like pancuronium have been used for the control of muscle spasms. Pancuronium is an inhibitor of catecholamine uptake and may worsen the autonomic instability. Vecuronium has been proposed as the neuromuscular blocking agent of choice in ventilated tetanus patients.²⁷ It is "cardiovascularly clean" but is relatively short acting and requires continuous infusion. We use vecuronium if neuromuscular blockade is required. The direct acting agent dantrolene has also been used.²⁸ The sedative agent propofol may also have useful muscle relaxant properties.^{24,29} It should not be used alone as it does not have any GABA activity or analgesic effect. Also the drug concentrations required to control spasms were closer to anesthetic than sedative doses and thus mechanical ventilation was more frequently required.²⁹

4. Control of Autonomic Dysfunction

The strategies used for management of autonomic dysfunction are unsatisfactory as there is no defined criterion for the diagnosis of autonomic instability. As with control of spasms, no one class of drugs or combination has been demonstrated to be consistently effective. The treatments discussed below illustrates some of the controversies.

Beta-Adrenergic Blocking Agents : Propranolol is the commonest drug used for the control of autonomic dysfunction. But it may produce hypotension, pulmonary edema and cardiac arrest at times. Labetolol for its combined alpha and beta effect has been used, but alpha-blocking effect is less effective. Esmolol (short acting beta blocker) reduces the catecholamine release and may have advantage over other beta-blockers.³⁰ However, it is expensive and is very short acting.

Morphine : Morphine acts centrally to reduce sympathetic tone to the heart and vascular system, resulting in decrease in heart rate and fall in blood pressure.³¹ But morphine acts on the gastro-intestinal

tract causing constipation and ileus, which may further compound the gastro-intestinal component of the autonomic instability.

Magnesium Sulfate : Magnesium inhibits the release of humoral and neuronal catecholamines and reduces the sensitivity of alpha-adrenergic receptors. It has been used to treat autonomic dysfunction with varying results. Its overdose may cause respiratory paralysis, sedation or complete anesthesia. It was inadequate alone but is an effective adjunct in controlling autonomic disturbances.³²

Baclofen : Intrathecal baclofen (a GABA agonist) has been reported to be useful in some series with varying success.³³ The technique is invasive, expensive and facilities for ventilation must be available at hand immediately.

Epidural Blockade : Lumbar epidural blockade with local anesthetic agents has controlled cardiovascular instability and reduced serum catecholamine concentration.³⁴ Either thoracic or lumbar route have been used.

Clonidine : Clonidine is a selective partial agonist for alpha₂ adrenergic receptors in the central nervous system. Acting centrally it causes hypotension and bradycardia. The precise mechanism of action is not fully understood but it is presumed to involve inhibition of sympathetic outflow and potentiation of parasympathetic activity, thus increasing the vagal tone. Clonidine also produces marked sedation and anxiolysis, decreases spontaneous motor activity and potentiates sedative and anesthetic action of other drugs. Oral, intravenous, intrathecal and transdermal preparations are available. Clonidine needs further investigation as a treatment modality for autonomic dysfunction in tetanus.^{35,36} We use propranolol or clonidine in patients having evidence of autonomic instability.

Other Drugs : Drugs with potential benefit include atropine (for autonomic dysfunction),³⁷ sodium valproate (for sedation),³⁸ angiotensin converting enzyme (ACE) inhibitors (for hypertension)³⁸ and adenosine (for arrhythmias).³⁹ To date their use has been largely experimental with clinical use restricted to isolated reports.

3. Supportive Treatment

The management of tetanus requires a multidisciplinary approach. Airway management involves early airway protection, anticipating the hypoxic insult that patients might suffer due to frequent spasms or drug induced respiratory failure. We intubate patients having frequent spasms, requiring high dose intravenous diazepam (> 60 mg/

kg/day) or those requiring neuromuscular blockade for uncontrolled spasms. There is no consensus on role of tracheostomy in these patients. Meticulous mouth care, chest physiotherapy and regular tracheal suction are essential to prevent atelectasis, lobar collapse and pneumonia. Adequate sedation is mandatory for such interventions in patients at risk for uncontrolled spasms. Our 8 patients (53.33%) required endotracheal intubation for a period of 6 - 14 days (mean duration - 10 days). Three of them subsequently underwent tracheostomy: one for uncontrolled laryngospasm and two because of prolonged intubation (14 days). Rest of the 5 patients was extubated uneventfully. Ventilatory support is often needed specially if neuromuscular blockade is required for uncontrolled spasms. We ventilated 6 patients: five for uncontrolled spasms and one for diazepam induced respiratory suppression. If rigidity and spasms are poorly controlled then we paralyze the patient and initiate controlled mode of ventilation. Later we wean off patients on modes that allow spontaneous respiratory efforts (synchronized intermittent mandatory ventilation, pressure support ventilation, continuous positive airway pressure).

Energy demand may be high in these patients due to muscular spasms, excessive sweating and sepsis. Enteral feeding should be established as early as possible. In those patients unable to tolerate enteral feeding, cytoprotection is best achieved by using sucralfate or ranitidine.

Patients who survive are particularly prone for secondary complications: nosocomial infection, bedsores, tracheal stenosis and gastrointestinal hemorrhage. Secondary infections are a frequent complication, most commonly encountered are ventilator-associated pneumonia, urinary tract infection and wound sepsis. Gram negative and *Staphylococcus aureus* infections are common. Maintaining adequate spacing between beds and general standards of cleanliness such as regular hand washing are effective measures. Respiratory complications from aspiration and hypoventilation are

common and may be reduced by early tracheostomy, avoiding nasogastric tubes whenever possible and nursing patient in a 15° - 30° sitting posture. The usual protocol for management of tetanus is given in Table 4.

There is little information about the follow-up schedule of discharged patients, particularly for cognitive function, though enuresis, mental retardation and growth delay has been reported in patients treated for severe tetanus.⁴⁰ Mortality even in tertiary care centers from India has been reported to be between 14 - 35%.^{5,22,41} Of our 15 patients, 5 died (33.33%), 3 of hospital acquired sepsis and 2 probably due to autonomic instability (sudden cardiac arrest in one and ventricular fibrillation in the other).

Severe tetanus remains a clinical challenge. Incomplete understanding of the mechanisms involved, failure to identify the ideal drug(s) and the inexperience of most intensivists in the management of this disease are the factors responsible. Most patients with tetanus are in developing countries where intensive care facilities are limited, may be with no provision for mechanical ventilation or invasive hemodynamic monitoring.

Finally it should not be forgotten that tetanus is completely preventable by active immunization: "Prevention is always better than cure".

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TABLE 4. Suggested Protocol for Tetanus Management

- Wound debridement, as indicated.
- Human tetanus immunoglobulin (tetglob) 5000 to 8000 IU intramuscularly and active immunization if required
- Antibiotic treatment with penicillin or metronidazole
- Sedation with diazepam (20-120mg/kg/day), with midazolam or clonazepam as alternative medications.
- Vecuronium and mechanical ventilation, if spasms are not controlled by sedation.
- For autonomic instability, propranolol, magnesium sulfate or clonidine can be used.

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