The child with severe tetanus

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Abstract
Tetanus is an infectious disease which cannot be totally eradicated because the spores of the infecting organism are ubiquitous. It is however entirely preventable by immunization. It is still a health problem in the low-income countries with high neonatal mortality rates reported. It is also a cause of childhood mortality. In its severe forms, it is a multi-systemic disease affecting the autonomic, respiratory, cardiovascular and renal systems requiring multidisciplinary management in a neonatal or paediatric intensive care unit. The course of the disease may be prolonged, and the late sequelae of the disease may contribute significantly to morbidity in the growing child.

INTRODUCTION AND EPIDEMIOLOGY
Tetanus is a vaccine preventable toxin-mediated highly fatal disease of the nervous system characterised by muscle rigidity and painful muscle spasms.

It is a disease of the poor, the uneducated and those with adverse social circumstances. In low-income countries, it is common in the neonatal period in newborns whose mothers did not have their routine tetanus immunization during pregnancy as well as unhygienic deliveries taking place at home with unsterile umbilical cord practices. Effective immunization has reduced the incidence of neonatal tetanus significantly in high-income countries.

The World Health Organization (WHO) estimated that neonatal tetanus caused death of 30,848 newborns in 2017 which was a 96% reduction from an estimated death of 787,000 newborns in 1988. As the universal coverage of vaccine increases, the prevalence of tetanus has been found to drop.

Worldwide, all countries are committed to Maternal and Neonatal Tetanus Elimination (MNTE). As tetanus cannot be eradicated, the initiative aims to reduce maternal and neonatal tetanus by ensuring immunization of children, mothers, women of reproductive age as well as promotion of hygienic deliveries and cord care practices. As at July 2019, 12 low-income countries had still not eliminated MNTE. There is continuing progress in these countries and it is hoped that many more will achieve total elimination in the near future.

Post-neonatal tetanus is also a cause of morbidity and mortality in children aged 1 – 10 years with a prevalence rate of 0.48% reported in North India and 0.67% reported in Southern Nigeria. Management of the severe forms should be in a paediatric intensive care unit (PICU). In spite of its availability in some low-income countries, mortality continues to be on the rise. Childhood vaccination especially the booster doses of the vaccine should be routinely administered to prevent the disease scourge.

PATHOPHYSIOLOGY
Tetanus is caused by Clostridium tetani, a motile, gram positive, spore-forming obligate anaerobe. It is ubiquitous; commonly found in soil but has also been found in human and animal faeces. The spores can survive for months to years and are resistant to boiling and disinfection. It can however be destroyed by autoclaving at 120°C for 15 minutes at 1 atmospheric pressure.

In infected or necrotic tissue, anaerobic metabolism occurs, allowing the organism to secrete two toxins: tetanoylsin and tetanospsamin.

Tetanoylsin damages the surrounding viable tissue and optimizes conditions for bacterial multiplication. It causes permeability changes in biological membranes causing cell lysis.

Tetanospsamin is responsible for the clinical syndrome of tetanus. It is one of the most lethal toxins known, having an estimated minimum lethal dose of 2.5ngkg⁻¹. It enters the nerve terminals through the lower motor neurons responsible for initiating voluntary muscular movements.
It then travels by retrograde axonal transport to the spinal cord and brainstem.

Here, the toxin exerts its effects by cleaving synaptobrevin, a vesicle-associated membrane protein which is responsible for release of neurotransmitters. The toxin primarily affects inhibitory neurons preventing the presynaptic release of gamma-aminobutyric acid (GABA) and glycine. These neurons keep overactive motor neurons from firing and also play a role in the relaxation of muscles after contraction. There is thus loss of inhibitory actions on motor and autonomic neurons. With this loss, there is uncontrolled muscle contractions as well as autonomic hyperactivity responsible for the ever-present features of muscle spasms and autonomic dysfunction.

Other theories have however been suggested to cause autonomic dysfunction including damage to the brainstem and hypothalamic nuclei. Autonomic dysfunction was considered to be only sympathetic overactivity, but studies with haemodynamic monitoring have shown that both sympathetic and parasympathetic systems are involved.

Once the toxins are affixed to the neurons, they cannot be neutralized by antitoxins. Recovery of nerve function is dependent on regeneration of new nerve terminals and formation of synapses which explains the prolonged duration of tetanus.

Localized tetanus occurs when the nerves supplying the muscle of the contaminated site is involved. With a high toxin load, there is haematogenous and lymphatic spread to multiple nerve terminals resulting in generalized tetanus. Cerebral neurons are spared because the toxins do not reach the cortical neurons by the retrograde axonal transport and do not pass the blood brain barrier to gain access from the bloodstream. Because of this, patients with tetanus are often conscious. Involvement of the lower cranial nerves has been suggested to result from their relation to area postrema on the floor of the fourth ventricle where the blood-brain barrier does not exist.

**Classification**

Four clinical types of tetanus have been described: Localized tetanus involves the muscles surrounding the portal of entry. There is a low toxin load and therefore spasms and rigidity are restricted to these group of muscles. Mortality is low. Cephalic tetanus is a form of localized tetanus involving the facial muscles. It occurs in tetanus following head wounds or otitis media. It rapidly progresses to generalized tetanus and has a high mortality. Neonatal tetanus is the most fatal form as it causes more than 50% of deaths from tetanus worldwide. It occurs in neonates and is usually generalized. Generalized tetanus is the most common form of tetanus found in children outside the neonatal period. It is also referred to as post-neonatal tetanus in children.

**Natural History**

Following injury and colonization of the bacilli, the first symptom of tetanus occurs within 7 – 10 days, with a range of 1 – 60 days. This is the incubation period (from injury to first symptom). This interval is a reflection of the distance the toxin travels to the nervous system and is related to the quantity of toxins released. The first symptom is often trismus (lockjaw) which is due to contraction of the masseter muscle. The onset time is from the first symptom to the first spasm and occurs within 1 – 7 days. A short incubation period and onset time are associated with severe disease and poor prognosis.

The features of tetanus are a triad of muscle rigidity (from increased muscle tone), spasms and when severe, autonomic dysfunction. The manifestations of tetanus assume a descending form; trismus or lock jaw (from masseter muscle spasm), neck stiffness, dysphagia, and

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**Figure 1:** Severe spasms with flexion of the arms in neonatal tetanus. Reproduced by permission from Department of Paediatrics, Lagos University Teaching Hospital (courtesy Dr O.O Majiyagbe)

**Figure 2:** Opisthotonus position in a child with severe tetanus. Portal of entry was a head wound which had healed at presentation
board-like rigidity of the abdomen are often early symptoms. Spasms of the facial muscles cause the typical wry smile – risus sardonicus. Rigidity of the neck muscles lead to retraction of the head while truncal rigidity and preponderance of extensor muscle contraction leads to opisthotonus posturing.

Spasms are excruciatingly painful and progressively affect other muscle groups with a convulsive-like appearance. They may occur spontaneously, or be triggered by touch, visual or auditory stimuli. Spasms may be severe enough to cause long bone fractures and tendon avulsions. Laryngeal spasms will cause acute airway obstruction with hypoxia and death ensuing. Spasms may persist for 2 – 3 weeks or may be longer. Autonomic dysfunction usually starts several days after the spasms and reaches a peak during the second week of the disease. In neonates however, it occurs during the first week of the illness possibly because of their short axonal length. Rigidity usually lasts beyond the duration of both spasms and autonomic dysfunction.

The affected neonate would have established sucking after birth, but stops sucking, is irritable and has a fixed wry smile on the face. This is followed by rigidity, spasms, fever and difficulty in breathing. There may be evidence of umbilical cord sepsis such as hyperaemic and foul-smelling umbilical cord. Death will occur by the end of the first week if management is not instituted.

Severity grading of tetanus

Several grading systems have been described which serve as an index of severity. The Dakar score is commonly used in neonates while the system reported by Ablett is the most widely used in older children.

Even with the advent of mechanical/artificial ventilators to manage the respiratory complications of severe tetanus, many children still die. This is from autonomic disturbances which can be life-threatening. It presents as labile hypertension, persistent tachycardia and vasoconstriction with sweating, bradycardia, cardiac arrhythmias, hypotension and fever. Autonomic storms may occur with marked cardiovascular instability; severe hypertension and tachycardia may alternate with profound hypotension and bradycardia with recurrent cardiac arrest. Other autonomic effects include profuse salivation and increased bronchial secretions, gastric stasis, ileus and diarrhea. Tetanus is a multi-systemic disease with its direct effects on some organ systems when severe:

Altered respiratory physiology

Ineffective cough mechanisms from rigidity and spasms lead to atelectasis, subsequent pneumonia and Type I respiratory failure. Pharyngeal and laryngeal spasms will cause life threatening airway obstruction and Type II respiratory failure. Muscular rigidity and spasms of the chest wall, diaphragm and abdomen lead to a restrictive defect contributing to the ventilation perfusion mismatch. Prolonged spasms as well as altered brain stem function may lead to sudden or repeated apnoea. The neonate often presents with apnoea. The inability to swallow saliva, profuse bronchial secretions, pharyngeal spasms, raised intraabdominal pressure, gastroparesis from autonomic dysfunction all increase the risk of aspiration.

Altered cardiovascular physiology

The effect on the cardiovascular system is from sympathetic nervous hyperactivity, toxic myocarditis and medullary effects.

Sympathetic nervous hyperactivity causes labile hypertension, tachycardia, arrhythmias, high oxygen consumption, peripheral vascular constriction, intense diaphoresis, pyrexia and increased urinary catecholamine excretion. It is integral in severe cases of tetanus. Cardiac output is high but there is low to normal systemic vascular resistance because of extensive vasodilatation in metabolically active muscles. Refractory hypotension unresponsive to fluids and vasopressors has been associated with a direct effect of the toxin on the myocardium – toxic myocarditis. Sudden cardiac failure has been associated with medullary damage in the brainstem. Pyrexia in the absence of infection has been attributed to disturbance of the temperature regulating center.

Altered renal physiology

There is a reduction in glomerular filtration rate and impaired tubular function due to alteration of renal blood flow from catecholamine surges, rhabdomyolysis from severe spasms, dehydration and sepsis.

<table>
<thead>
<tr>
<th>Prognostic factor</th>
<th>Score 1</th>
<th>Score 0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incubation period</td>
<td>&lt;7 days</td>
<td>≥7 days or unknown</td>
</tr>
<tr>
<td>Onset time</td>
<td>&lt;2 days</td>
<td>≥2 days</td>
</tr>
<tr>
<td>Entry site</td>
<td>Umbilicus, burns, open fracture, surgical wound, intramuscular injection</td>
<td>All others plus unknown</td>
</tr>
<tr>
<td>Spasms</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>Fever</td>
<td>&gt;38.4°C</td>
<td>&lt;38.4°C</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>Adults &gt;120 beats/min</td>
<td>Adults &lt;120 beats/min</td>
</tr>
<tr>
<td></td>
<td>Neonates &gt;150 beats/min</td>
<td>Neonates &lt;150 beats/min</td>
</tr>
<tr>
<td>Total score</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

A score of 0 – 1 indicates mild illness with a mortality of up to 10%
A score of 2 – 3 indicates moderate illness with a mortality of up to 20%
A score of 4 indicates severe illness with a mortality of up to 40%
A score of 5 – 6 indicates very severe illness with up to 50% mortality
### MANAGEMENT

This must be done either in a neonatal intensive care unit or paediatric intensive care unit for the older child. These are however limited in most hospitals in the low-income countries contributing to the high mortalities reported.

The management aims to provide supportive care till the neurotoxin bound to the nervous tissue has been eliminated. This is done by:

- Neutralization of the circulating toxins
- Elimination of the source of the toxins
- Control of rigidity, spasms and management of complications

#### Neutralization of circulating toxins

As the damage caused by tetanospsammin that has entered the nervous tissue is irreversible, emphasis is placed on neutralizing the circulating toxins before it enters the nervous system. Human tetanus immune globulin is the preferred drug and is given at a dose of 150units.kg\(^{-1}\) intramuscularly. When unavailable, equine anti-tetanus serum at a dose of 500-1000units.kg\(^{-1}\) should be given intramuscularly or intravenously. The latter requires pretesting before administration. Antitoxin should be given as soon as diagnosis is made. Some authors have explored administering these immunoglobulins intrathecally. This has however been found to have no added benefit.

#### Elimination of the source of the toxins

The wound, if obvious, should be surgically debrided. Intravenous (IV) metronidazole (15mg.kg\(^{-1}\)stat then 7.5mgkg\(^{-1}\)every 8 hours for 10 days) is preferred to IV Penicillin G (100,000 – 200,000IU. kg-1day\(^{-1}\) IV in 2 divided doses). Penicillin G causes a non-competitive, voltage dependent inhibition of GABA receptors. With this, it can cause seizures and potentiate the action of tetanospsammin. Macrolides, clindamycin, and chloramphenicol are also effective alternatives. With neonatal tetanus, broad spectrum antibiotics such as the third generation cephalosporins are often added because the neonate usually presents with sepsis.

#### Control of rigidity and spasms

Benzodiazepines are the standard therapy for controlling muscle spasms in tetanus and have gained popularity over other agents due to their combined muscle relaxant, anticonvulsant, sedative and anxiolytic effects. Benzodiazepines modulate GABA transmission and increase pre-synaptic inhibition. The most popular is diazepam which is cheap and readily available in low income countries where tetanus is still a significant health problem. It is administered at a dose range of 0.1 – 10mg.kg\(^{-1}\) per dose. It has a large volume of distribution and may lead to prolonged recovery when the doses are tailed off. Midazolam, a short acting benzodiazepine compared to diazepam, is favored in critical care for sedation. It is theoretically a better option than diazepam for tetanus. There is however limited evidence of its use in the literature. Anticonvulsants such as phenobarbitone (5mg. kg\(^{-1}\) per day) and phenothiazines usually chlorpromazine (0.5mg.kg\(^{-1}\)) are often added as adjunctive sedatives to diazepam. Propofol may be used in adults with tetanus because of its excellent sedative effects and it does not accumulate. It is however avoided in neonates and children as a sedative because of untoward metabolic, cardiac and renal effects. In severe tetanus, spasms are often not controlled even with high doses of these agents and neuromuscular blockade will be required.

Endotracheal intubation with mechanical ventilation should be undertaken for all cases of severe tetanus. This should be done with rapid sequence induction using IV suxamethonium (2mg.kg\(^{-1}\)) as the child is prone to aspiration. This can be continued with intermediate muscle relaxants like IV atracurium (0.5mg.kg\(^{-1}\)) or vecuronium (0.1mg.kg\(^{-1}\)). Pancuronium (a long acting muscle relaxant) may worsen autonomic instability by inhibiting catecholamine reuptake so should be avoided. Prolonged usage of these amino steroid muscle relaxants has been associated with critical illness neuropathy and myopathy. Tracheostomy should be performed in patients requiring intubation for more than 5 days.

Intrathecal baclofen (a GABA-B receptor agonist) and dantrolene (a skeletal muscle relaxant) have been investigated but limited to a few case series and are not readily available in the resource-poor setting.

#### Control of autonomic dysfunction

Magnesium sulphate is an effective adjunct in relaxation, sedation, and controlling the autonomic disturbances in tetanus. It is a pre-synaptic neuromuscular blocker, reduces catecholamine release from nerves and the adrenal medulla and reduces receptor responsiveness

### Table 2: Summary of complications

<table>
<thead>
<tr>
<th>Body System</th>
<th>Complication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autonomic dysfunction</td>
<td></td>
</tr>
<tr>
<td>Aspiration, laryngospasm, airway obstruction</td>
<td>Respiratory</td>
</tr>
<tr>
<td>Hypoxia, apnoea, Type I and II respiratory failure, Acute respiratory distress syndrome (ARDS), complications of prolonged mechanical ventilation</td>
<td>Cardiovascular</td>
</tr>
<tr>
<td>Tachycardia, hypertension, ischaemia, hypotension, bradycardia, arrhythmias</td>
<td>Renal</td>
</tr>
<tr>
<td>Stasis, ileus, haemorrhage</td>
<td>Gastrointestinal</td>
</tr>
<tr>
<td>Renal failure, stasis and urinary tract infection</td>
<td>Miscellaneous</td>
</tr>
<tr>
<td>Stasis, ileus, haemorrhage</td>
<td>Weight loss, thromboembolism, sepsis, multi organ dysfunction syndrome, fractures due to spasms</td>
</tr>
</tbody>
</table>

https://resources.wfsahq.org/update-in-anaesthesia
to released catecholamine. Its use has been well described in literature. It reduces the requirements of other sedatives and muscle relaxants in controlling rigidity and spasms. It is administered at a dose of 100 – 400mg.kg\(^{-1}\)hr\(^{-1}\) in children. In neonates a loading dose of 50mg.kg\(^{-1}\) followed by a maintenance dose of 30 – 50mg.kg\(^{-1}\)hr\(^{-1}\) is given. By antagonizing calcium metabolism, magnesium causes weakness and paralysis in overdose. Monitoring of serum magnesium levels is important to prevent this. The normal serum magnesium level is 0.7 – 1.0mmol\(^{-1}\), while an acceptable therapeutic level is 2 – 3.5mmol\(^{-1}\). This laboratory investigation may not be available in the resource poor setting thus limiting its use. Monitoring of the deep tendon reflexes, urinary output as well as respiratory rate in the spontaneously breathing child is imperative as a clinical index of toxicity. The use of invasive blood pressure monitoring, if available may facilitate early recognition of autonomic dysfunction with prompt interventions instituted.

Opioids like morphine and fentanyl have been used in the management of autonomic dysfunction. They induce peripheral arterial dilatation by reflex reduction in sympathetic \(\alpha\)-adrenergic tone, through alteration of the sympathetic efferent discharge in the central nervous system.

Beta-blockers (particularly long-acting agents like labetalol) have been implicated in sudden cardiac death and are not recommended. The short acting beta-blocker, esmolol, may be used to manage tachycardia and hypertension, where invasive monitoring is available. It is also not readily available.

The alpha-2 agonists, clonidine and dexmedetomidine, inhibit the release of norepinephrine from prejunctional nerve endings and may have a useful role.

**Supportive care**

This is crucial to the outcome of children admitted with tetanus. A multidisciplinary approach is essential. Poor nutrition with subsequent weight loss occurs rapidly because of dysphagia, altered gastrointestinal function and high metabolic rate. Enteral nutrition should be established early via nasogastric tube or percutaneous gastrostomy. Fluid and electrolyte imbalance should be corrected because of fever, diaphoresis and excessive secretions. Prevention of respiratory complications includes meticulous mouth care, chest physiotherapy and regular orotracheal or tracheostomy tube suctioning. Steps should be taken to prevent ventilator associated pneumonia. Nosocomial infections are common because of the prolonged course of the disease and remains a cause of mortality. Chest and limb physiotherapy may be limited in the early stages of the disease as it provokes spasms. Other supportive measures include prevention of venous thromboembolism, ulcers and pressure sores.

### Late Sequelae of Tetanus

Tetanus has been associated with significant morbidity in children who survive. Microcephaly, mental retardation, motor disabilities and growth failure have been observed in children who recovered from neonatal tetanus. Transient or permanent disorders such as irritability, memory and sleep disorders, learning disabilities have also be reported in children who recovered from post-neonatal tetanus. In the latter group, electroencephalogram abnormalities were observed to be higher than in the normal population.

### Prevention

A child that survives tetanus is still prone to tetanus in the future because the infection does not confer any immunity. Active immunization must be performed with Diptheria Pertussis Tetanus (DPT) vaccine given at age 6weeks, 10weeks, 14weeks of life, 18months and 5years. Immunization of pregnant women and women in the reproductive age is essential. There should be prompt and adequate care of wounds with hygienic care of the umbilical cord in newborns. Children with tetanus prone wounds need to be reviewed to check if they will benefit from passive immunization.

### Conclusion

Tetanus is a third world disease requiring first world facilities in its management. Primary prevention is key especially in the low-income countries instead of management and rehabilitation of its sequelae.

### REFERENCES

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Total parenteral nutrition (TPN) is continued till return of bowel function which may take several weeks especially in gastroschisis. Where TPN is not available, infusions of amino acids and lipids have been utilised with varied responses. Fluid, electrolyte, glucose and temperature maintenance must be addressed during this time.

CONCLUSION
Abdominal wall defects in neonates may be small or large, with an intact or ruptured sac. The size and type of the defect determines the severity of heat and evaporative losses and the risk of infection. Operative management may be primary or staged closure. Intra-abdominal compartment syndrome and hypothermia are major intra-operative concerns to the anaesthetist. Some neonates will need post – operative ventilation. Prenatal screening and protocol for management should be adopted in resource – poor countries to ensure a good outcome. Optimal management will require a multidisciplinary approach with an anaesthetist, intensivist, surgeon, neonatologist and obstetrician.

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REFERENCES