

Adult Tetanus in the 21st Century: Where are we? Case Series and Review

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Abstract

Original Research Article

Objective: To review cases of severe adult tetanus admitted to intensive care unit (ICU) and describe clinical features, etiologic factors and outcome of 2 patients with the diagnosis of severe adult tetanus. **Study Design:** A retrospective case series. **Methods:** Medical records of patients admitted with severe tetanus to adult intensive care Hospital Raja Perempuan Zainab 2 (HRPZ 2) in 2018 were reviewed. **Results:** 2 patients were identified, aged of 18 years old and 72 years old. Both patients presented to our care after 14 days of alleged cut by scrap metal with clinical features of severe tetanus and multiorgan impairment. However, the elderly patient developed a life-threatening autonomic disturbance. Despite good improvement of their clinical condition, the elderly patient was discharged from intensive care unit after 41 days of admission, whereas the younger patient was discharged from intensive care unit after 7 days of admission. **Conclusion:** Adult tetanus will remain a relevant and important disease in the 21st century. With the advancement of care in the intensive care unit, there is a shift in a cause of death that is from acute airway obstruction, respiratory failure and renal failure as a prominent cause of death to a complication of autonomic disturbance and intensive care related complications with include nosocomial infection, sepsis and complications of prolonged stay in intensive care unit. Lack of definitive randomized control trial, with a significant lack of familiarity and compliance to tetanus prophylactic among physicians will remain as a major issue in managing tetanus in the 21st century. This issue is further complicated by a gradual loss of immunity to tetanus among elderly population.

Keywords: Adult tetanus, tetanospasmin, *Clostridium tetani*, complications.

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INTRODUCTION

The word tetanus derived from Greek words – ‘Tetanos’ which mean ‘to contract’ or ‘to stretch’. Tetanus symptom is caused by Gram-positive bacillus (*Clostridium tetani*) which produces its effects through the release of its two powerful exotoxins called tetanolysin and tetanospasmin; although the exact role of this exotoxin to the organism itself is still unknown. Despite being first described in Egyptian period over 3000 years ago, tetanus infection still remains a major health problem in the developing countries and still a relevant disease in the developed countries.

Until now, despite the administration of passive immunization since 1893 and aggressive vaccination programme since 1923, the incidence and mortality of worldwide tetanus remain high. This is particularly important among adolescent and adult male since a great effort was focused on the eradication of

maternal and neonatal tetanus, but much less attention has been given to adolescent and adult male. According to the World Health Organization (WHO) recommendations, a series of three tetanus-toxoid containing vaccine doses should be given in infancy, followed by booster doses at the age of school entry, in adolescence and in adulthood to induce longer-term immunity [1, 2]. However, this vaccination regime is more concentrated on the female population during their reproductive years as compared to the male population. In current practice, women will receive tetanus booster vaccinations during their antenatal care. However, adult and adolescence male remain at risk for tetanus as there is no additional vaccination protocol or booster in place to ensure their post-infancy vaccination.

We report our experience in managing male adolescent and elderly patients with severe tetanus, describing the clinical features, complications and

outcome. We also discussed factors which might lead to the development of severe tetanus in our patients and the general population.

METHODS

Two adult males were identified, with the age of 18 years old and 72 years old. Both sustained a minor cut at their foot from contaminated scrap metal. Coincidentally, both patients did not seek any medical treatment for their wound and both were admitted to our adult intensive care unit 2 weeks after the alleged wound. Both patients demonstrated some specific and non-specific signs and symptoms of tetanus with multiorgan impairment. Importantly, the elderly patient who was also a diabetic patient presented with a life-threatening autonomic disturbance (autonomic storm). Both had improvement in their clinical conditions at the time of discharge from our intensive care unit, but the elderly male patient has a significant delay in discharge due to the severity of his tetanus and complications from prolonged stay in intensive care.

Case Presentation

Case-1

MA was an 18-year-old Malay boy, not known to have any medical illness. He presented to a district hospital with a one-day history of back and neck stiffness, associated with fever, upper respiratory tract infection, diarrhoea and poor oral intake. The patient had two weeks history of alleged cut by scrap metal over his right big toe but not seeking immediate medical attention for that wound. On physical examination, the patient was alert and conscious with stable hemodynamic parameters. Neurological examination revealed an increase in muscle tone with hyperreflexia in all his four limbs. Babinski test was down going. There was also an infected wound size measuring 3x3 cm over his right big toe.

On the same day of admission, the patient developed difficulty in breathing and was intubated for airway protection. The patient was then referred to Hospital Raja Perempuan Zainab 2 (HRPZ2) intensive care unit (ICU) with the diagnosis of severe tetanus. A single dose of 3000IU Tetanus Immunoglobulin was injected around the infected wound and his antibiotic was changed from intravenous Augmentin to intravenous Penicillin. Intermittent intravenous diazepam and magnesium sulphate were administered for sedation and prevention of muscle spasm. In the intensive care unit, the patient developed severe muscle spasms complicated with opisthotonos and meningism like symptoms. He was treated with severe tetanus, acute kidney injury, thrombocytopenia secondary to sepsis which may originate from his infected right big toe wound.

He was extubated two days after his ICU admission and was able to be discharged from the unit

after 7 days later with good recovery and asymptomatic from the muscle spasm.

Case-2

WJ was a 72-year-old Malay gentleman with a background history of hypertension and diabetes mellitus. Presented to a district hospital with an acute onset of slurred speech. He had no other neurological deficit. The patient was then referred to Hospital Raja Perempuan Zainab 2 (HRPZ2) with the provisional diagnosis of cerebrovascular accident.

His brain CT scan revealed a multifocal multi-stages infarction involving anterior limb of the left internal capsule and basal ganglia of recent infarction with the posterior limb of both internal capsules of lacunar infarction. He was started on both antiplatelet and anticoagulant. On the second day of admission to the hospital, the patient developed dysphagia and trismus. Clinical examination revealed an increase in muscle tone with hyperreflexia in all of his four limbs. An infected wound was noted over his right foot. On further questioning, patient admitted of having a cut by scrap metal at his right foot 2 weeks prior to this admission but did not seek any medical attention. He was referred to the intensive care unit (ICU) for close observation. In the ICU, the patient received 3000 IU intramuscular Tetanus Immunoglobulin, intravenous Penicillin with metronidazole, magnesium sulphate infusion and daily dressing of his wound. However, on the second day of his ICU admission, he developed severe autonomic disturbances with multiple episodes of intermittent hypotensive and bradycardic (Blood Pressure (BP) of 80/50 mmHg, and pulse rate of 30 beats/min) alternating with hypertensive episodes (systolic BP of 200 mmHg, diastolic BP of 110 mmHg). He even developed an episode of severe bradycardia requiring cardiopulmonary resuscitation (CPR) for two minutes before reverted to sinus rhythm.

Subsequently he developed episodes of spontaneous upper trunk muscle spasms which were aggravated during suctioning of tracheal secretion. The spasm were aborted with intravenous midazolam and diazepam supplemented with magnesium sulphate infusion. In the ICU he developed non-oliguric acute kidney injury, paroxysmal atrial fibrillation, upper gastrointestinal bleeding (with Forrest III ulcer), and nosocomial infection (Extended Spectrum Beta-Lactamase (ESBL)-producing *Klebsiella pneumoniae*, Multidrug resistance (MDR) *Pseudomonas aeruginosa* and fungemia). Tracheostomy was performed on the 20th day in view of prolonged ventilation with poor conscious level (Eye opening: 1, Motor response: 1, Verbal response: T). An electroencephalogram (EEG) after tracheostomy reveals theta range activities which was consistent with mild encephalopathy. He was discharged to general ward from the unit 40 day after the ICU admission.

DISCUSSION

Tetanospasmin, one of the released exotoxins by *Clostridium tetani* is responsible for producing the clinical syndrome of tetanus. Once released, tetanospasmin will spread to the nearby underlying tissue and binds to the gangliosides on the membrane of local nerve terminals. If the concentration of tetanospasmin is significantly high, tetanospasmin will enter the bloodstream. From the blood circulation tetanospasmin will diffused and bind to nerve terminals throughout the body. Tetanospasmin will then internalized and transported to the cell body, affecting the motor nerves and will be followed by the sensory and autonomic nerves [3, 4]. Tetanospasmin will also spread to brainstem and midbrain through retrograde intraneural transport. Through the cell body, tetanospasmin can diffuse out, affecting and entering nearby neurones. When spinal inhibitory interneurons are affected, tetanus symptoms will occur [5].

The effects of tetanospasmin resulted from prevention of the release of neurotransmitters after it was internalized into the inhibitory neurones. The predominant effect is on the inhibitory neurones, which is inhibiting the release of glycine and gamma-aminobutyric acid (GABA) [6]. Interneurons inhibiting alpha neurones are first affected leading to lost of inhibitory control of motor neurones. This will be followed by ganglionic sympathetic neurones in the lateral horns and the parasympathetic centres. Uncontrolled disinhibited efferent discharge from motor neurones in the cord and brainstem will lead to intense muscular rigidity and spasm. Disinhibited autonomic discharge of the sympathetic and parasympathetic nervous system will lead to the disturbances in autonomic control, which is characterised by sympathetic overactivity and excessive plasma catecholamine levels [6].

Important to note that neuronal binding of tetanospasmin to the neurones is irreversible and it cannot be neutralized by the administration of tetanus antitoxin. This irreversible binding will cause the neurones unable to release its neurotransmitter leading to the characteristic signs and symptoms of tetanus. Recovery of nerve function from tetanospasmin requires the development of new nerve terminals and formation of new synapses. This might explain the prolonged effect of tetanus syndrome in the affected patient.

Data from the Global Burden of Disease Study in 2015⁷ revealed 56 743 worldwide mortality due to tetanus in 2015, in which 19 937 mortality occurred in neonate's population, and 36 806 mortality occurred in older children and adults. 45% of neonatal tetanus mortality occurred in South Asia, and 44% in Sub-Saharan Africa. 47% of non-neonatal tetanus mortality occurred in South Asia, 36% in Sub-Saharan, and 12% occurred in Southeast Asia. Interestingly, this data also

showed that age-standardised mortality from tetanus was higher among males' population as compare to female's population globally. This finding was further supported by a study done by Marulappa *et al.*, [8] in which out of the 512 cases of tetanus in their study (age more than 15 years old), 379 patients (74%) were males and only 133 patients (26%) were females. This data was almost comparable to the data from the developed country; data from Epidemiology of Tetanus in the United States⁹ revealed that tetanus occurs primarily among older tetanus. From 2001 to 2016, three neonatal tetanus cases and 459 non-neonatal tetanus cases were reported to the National Notifiable Diseases Surveillance System (NNDSS). The median age of patients contracting non-neonatal tetanus was 44.0 years (range: 2 to 95 years old). Interestingly, 60% of cases occurred among males⁹. Summary from these studies are risk for both tetanus disease and mortality was higher among persons aged more than 65 years old; ages of the patients and the presence of complications had a statistically significant relationship with respect to the outcome (survival versus death), and incidence is much higher among adult males as compared to adult females with the possible explanation of occupational exposure and relatively lower vaccination coverage.

To date, with the advancement of treatment and monitoring in intensive care, mortality of adult tetanus remains unchanged. The overall mortality rate in patients with tetanus aged more than 60 years old remain more than 50%. A common cause of death is directly related to severe tetanus manifestations which include exhaustion, autonomic disturbances, and complications from intense and prolong muscle spasms (particularly asphyxiation, pneumonia, rhabdomyolysis and pulmonary emboli). In the United States, the mortality rate in adult tetanus for patient below 30 years of age may approach zero, however, the risk of mortality for adult tetanus in patients more than 60 years of age is 52%. Current World Health Organization (WHO) recommendations [11] for the management of tetanus include close inpatient monitoring, administration of immune globulin, sedation, analgesia, wound toilet and hygiene and more importantly good airway support. However, despite an increased provision of care as recommended by World Health Organization (WHO), there is still no significant reduction in overall mortality among adult tetanus (55.4% versus 40.3%, $p=0.069$) which has been showed by Aziz R *et al.*, [12]. Interestingly, there was also no difference in 7-day ICU mortality. What more important is that the analysis of the causes of death in this study revealed a sharp decrease in mortality related to airway compromise but there is a significant increase in mortality due to nosocomial infection, sepsis and complications related to prolonged intensive care in intensive care unit (ICU).

In developing countries, without adequate facilities for prolonged intensive care and ventilatory

support, the mortality rate from severe tetanus may exceed 50% in which airway obstruction, respiratory failure, and renal failure as prominent causes of mortality. In developed countries, modern intensive care can significantly prevent mortality from acute respiratory failure but as a result, in severe tetanus, autonomic disturbance becomes more apparent. As severe tetanus generally requires intensive care unit admission for approximately 3 to 5 weeks, important complications related to intensive care unit (ICU) management include nosocomial infections, particularly ventilator-associated pneumonia, generalised sepsis, thromboembolism, and gastrointestinal haemorrhage [10].

With the unchanged mortality rate of adult tetanus and a significant shift in the cause of death, several considerations need to be highlighted regarding the causes of high incidence and mortality among adult elderly tetanus, particularly to the adult male tetanus.

Throughout these years, the principles of managing non-neonatal tetanus were almost remain the same. Cook *et al.*, [10] in 2001 has outlined three principles in managing tetanus infection. These include destroying the organism that present in the body in order to prevent the release of further tetanus toxin; neutralisation of the toxin circulating in the body, outside the central nervous system; and minimizing the effects of toxin which already in the central nervous system. The component of this management principle are neutralization of unbound circulating toxin using human anti-tetanus immunoglobulin; removal of the source of infection through administration of antibiotics and to eradicate locally proliferating bacteria *Clostridium tetani* at the wound site; control of muscle rigidity and spasms through avoidance of unnecessary stimulation, providing sedation with benzodiazepine supported with anti-convulsant, propofol sedation, neuromuscular muscle relaxants and airway support using positive pressure ventilation; and control of autonomic disturbance using clonidine, magnesium sulphate, sodium valproate, angiotensin converting enzyme inhibitors, dexmedetomidine and adenosine. Supportive intensive care treatment which include early enteral nutrition, management and prevention of infective complications of prolonged critical illness including nosocomial infection, ventilator-associated pneumonia, prevention of respiratory and airway complications and adequate sedation is also mandatory. Other important measures include prophylaxis of venous thromboembolism, gastrointestinal stress and bleeding, management and prevention of pressure sores and importantly psychological support.

Due to its rarity in modern medicine, there is a potential for a delay in the diagnosis of tetanus as many physicians may not consider the diagnosis of tetanus until the manifestations of tetanus become overt. This is further aggravated by the delayed in seeking medical

attention by patients who sustained tetanus-prone wound or injury. Undoubtedly, without timely diagnosis and proper treatment, severe tetanus may become fatal with a high mortality rate. However, current treatments for tetanus are still relied on evidence-based strategies and many of the treatment options have not been assessed with a randomized clinical trial due to both logistical and ethical limitations. A review article written by Rodrigo *et al.*, [13] describe the lack of evidence of benzodiazepines for its superiority as a standard treatment for sedation and reducing spasm. Furthermore, despite a widely use of magnesium sulphate infusion to reduces muscle spasm and autonomic dysfunction, evidences suggest that magnesium sulphate infusion may not be suitable to be use as a sole therapy because it fail to provide mortality benefit with an inadequate statistical strength to demonstrate its use on positive impact in ICU stay. The use of intravenous magnesium sulphate may be reasonable and should be considered depending on the clinician judgement [13]. Intrathecal baclofen has also been suggested as an effective option to relieve spasms until the recovery phase. However, this is limited to a few case series and its use is further limited due to the cost and the risks of introducing concurrent central nervous system infection¹³. The benefit reported with dantrolene, botulinum toxin (for local form of spasms) in reducing muscle spasms and that of neuraxial (epidural) blockade and clonidine to reduce autonomic dysfunction are only limited to some case series and cannot be recommended without further evidence [13]. The route of administration of immunoglobulins is still conflicting in two meta-analyse studies. Although administrations of immunoglobulins are proven to be beneficial, the best route of immunoglobulins administration either through an intramuscular injection alone or through intrathecal administration with an intramuscular injection is still debatable. Finally, the use of antibiotic metronidazole in tetanus has a theoretical advantage over penicillin uses in which penicillin can potentially facilitate tetanospasmin activity. However, there are no trials to suggest that antibiotic use is beneficial in tetanus and evidence from a randomized controlled trial shows no benefit of choosing metronidazole over penicillin. Until now, either penicillin or metronidazole may be used as the antibiotic of choice in treating tetanus (expert opinion) [13].

Immunological memory which is mediated by antibodies is the hallmark of immunity. However, the longevity of protective immunity is heterogeneity in the responses of different individuals. Serological surveys done by Reid *et al.*, [14] in 1996 revealed an increasing proportion of the population with inadequate immunity as age increases; 49 – 66% of patients over 60 years old had antibody level for tetanus below the protective level. Among these elderly population, some had never been vaccinated, while others might have lost their immunity to tetanus. A more recent study done by Antia

et al., [15] in 2018 found that for the first 25 to 50 years, virtually all individuals have protective antibody against tetanus, respectively, but about 10% of the population subsequently lose their protective immunity per decade against tetanus. In 2016, Hammarlund *et al.*, [16] found that antibody response to tetanus declined with an estimated half-life of 14 years (95% confidence interval, 11-17 years). Using mathematical models combining antibody magnitude and duration, their study predicted that 95% of the population will remain protected against tetanus for more than 30 years without requiring further booster vaccination. However, in the same study, Hammarlund *et al.* revealed that of the 13 subjects lacking tetanus-specific immunity (< 0.01 IU/mL), 11 of the 13 subjects (85%) were more than 60 years old. These results indicate that individuals at older than 60 years old have an increased likelihood of a lack of immunity to tetanus. These can be explained either by not receiving full childhood vaccination series or probably as a result from age-related immune senescence in which antibody responses decay more rapidly with advanced age.

Tetanus-prone wounds include burns or wounds that require surgical intervention that is delayed for more than six hours, burns or wounds that show a significant degree of devitalized tissue, a puncture-type wound, particularly where there has been contact with soil or manure, wounds containing foreign bodies, compound fractures and wounds or burns in patients who have systemic sepsis. The need for active immunisation, with or without passive immunization, depends on the condition of the wound and also patient's immunization history. However, due to the rarity of the tetanus infection especially in the developed countries, there is a significant lack of familiarity and compliance to tetanus prophylactic guidelines among physicians treating patients with tetanus-prone wound. A study of tetanus prophylaxis in the emergency department [17] revealed that only 57% of patients presenting with wounds were provided with appropriate tetanus prophylaxis; and 35% of them were failed to receive indicated tetanus vaccination, or vaccination and tetanus immunoglobulin, and 8% of the patients received unnecessary measures. More importantly, none of the patients who most in need of prophylaxis (i.e., those without a history of primary immunisation presented with tetanus-prone wounds) were treated correctly. Furthermore, Talan *et al.*, [18] also revealed a significant lack of appreciation of the importance of a primary tetanus immunisation series among the physicians when accessing and managing tetanus risk by the absence of recorded information about primary vaccination in 80% of medical records. All these findings are consistent with tetanus surveillance data which showed that among reported tetanus cases, those who sought medical attention for their antecedent wounds, only fewer than 60% received indicated tetanus toxoid [19].

CONCLUSION

Adult tetanus will remain a relevant and important disease in the 21st century. Incidence of tetanus infection among adult and elderly male patients is still high with a significantly high risk of morbidity and mortality. With the advancement of care in the intensive care unit, there is a shift in a cause of death that is from acute airway obstruction, respiratory failure and renal failure as a prominent cause of death to a complication of autonomic disturbance and intensive care related complications which include nosocomial infection, sepsis and complications of prolonged stay in intensive care unit. Lack of definitive randomised control trial in improving the management of tetanus infection, with a significant lack of familiarity and compliance to tetanus prophylactic among physicians treating patients with the tetanus-prone wound will remain as a major issue in managing tetanus in the 21st century. This issue is further complicated by a gradual loss of immunity to tetanus among the elderly population.

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Compliance with Ethics Guidelines

Abdul Karim Othman, Mohd Nazri Ali, Wan Nasrudin Wan Ismail, Mazelan Omar, Nurul Aimi Mustapha and Mohd Shazli Deraman@Yusof declare that they have no conflict of interest. Patient anonymity was preserved, and this article does not contain any studies with animal subjects performed by any of the authors.

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