UPMC REHAB GRAND ROUNDS

FALL 2024

BEST HOSPITALS U.S.News & WORLD REPORT REHABILITATION 2024-2025

All Locked Up: The Treatment of Generalized Tetanus

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Clinical Vignette

A previously healthy, unvaccinated 9-year-old Amish male was running barefoot in a field when he stepped on a rusted wire. He had some pain and bleeding from the puncture wound, but otherwise felt well. Over the next three to four days, he developed shoulder stiffness. This was minor at first, but about a day after starting the pain began to worsen. The day prior to the presentation he continued with shoulder pain but also had trouble moving his neck. He tried to eat but had a lot of difficulty swallowing. In addition, he had trouble managing secretions and was drooling. When asked, he denied pain with swallowing and said he felt that he could not swallow. Due to inability to eat or drink very much over 24 hours, the family took him to the emergency room.

Upon arrival in the emergency room, in addition to the neck stiffness and drooling he also was exhibiting difficulty walking. Mom noted he was holding his body in awkward positions which had worsened over the past day. He was also having difficulty getting up from bed on his own and going to the bathroom. He was not as talkative as usual. Examination in the emergency room revealed hypertension (BP 128/73 — normal for age is SBP 100), tachycardia to 115. He had muscle rigidity with neck extension, arms flexed and partially folded in front of him. He was unable to move his neck in any direction. He had normal tone in his legs. He was unable to elicit a swallow. Based on examination findings of trismus, muscle rigidity, and autonomic instability in an unvaccinated individual with recent history of puncture wound from rusted wire, there was concern for generalized tetanus infection.

The patient was treated with metronidazole, given tetanus antitoxin, and vaccinated for tetanus. He was taken to the operating room where surgical debridement was done for his wound. He was started on oral diazepam with minimal relief or improvement in his pain and rigidity. His muscle rigidity and spasticity continued to worsen throughout his hospital stay, with development of opisthotonic posturing on hospital day 2. He was transferred to the pediatric intensive care unit where he was intubated for airway protection. He was also paralyzed with cisatracicurium due to the severity of his muscle rigidity, which he required for about 20 days.

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Disclosures

Drs. Zuziak, Kremm, and Godbold report no relationships with proprietary entities producing health care goods and services.

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Around hospital day 5 he developed dysautonomia characterized by facial flushing, hypertension, pupillary dilation, and tachycardia, for which dexmedetomidine was added and eventually transitioned to enteral clonidine. He experienced labile blood pressures with intermittent need for norepinephrine. A magnesium infusion was trialed but did not help his dysautonomia, therefore, it was discontinued. He was intubated for 25 days before successful extubation. At the time of extubation, benzodiazepine infusion had been discontinued and his spasms were being managed with enteral diazepam 5mg (0.16mg/kg/dose) every 6 hours. However, his lower extremity spasticity/rigidity persisted, he had little facial movement, and was dependent on a nasogastric tube for nutrition. Pediatric rehabilitation medicine (PRM) was consulted for tone management, dysphagia and impaired functional mobility as compared to the patient's baseline.

Pathophysiology

Tetanus is a vaccine preventable and life- threatening disease caused by tetanus toxin (tetanospasmin) produced by the spore-forming bacteria Clostridium tetani, a gram-positive anaerobic rod. The spores of this bacteria require anaerobic conditions, and survive in dust, dirt, and manure, before they can infect humans through contamination of wounds. Two exotoxins are produced – tetanolysin and tetanospasmin, with the latter being the one which results in the clinical manifestations of tetanus. The tetanospasmin will disseminate throughout the body via the bloodstream and lymphatic system and cause neuromuscular dysfunction. It is a very potent toxin, with a minimum lethal dose of 2.5ng/kg.

The tetanus toxin works in a fashion similar to that of botulinum toxin. The tetanus toxin is a zinc-dependent metalloproteinase that first binds at the presynaptic membranes of neuromuscular junctions. This can cause initial flaccid paralysis, like botulinum toxin, due to interference with acetylcholine release from the presynaptic neuron at the neuromuscular junction. However, unlike botulinum toxin, the tetanus toxin undergoes retrograde transport in the axons of lower motor neurons to reach the spinal cord or brain stem. Once in the central nervous system, it is taken up by the nerve terminals of inhibitory GABAergic and glycinergic neurons. Within inhibitory neurons, the tetanus toxin cleaves a protein (synaptobrevin/ vesicle-associated membrane protein, VAMP) which is a part of the SNARE complex needed for synaptic vesicle docking. Interruption in the SNARE complex within inhibitory neurons prevents exocytosis of vesicles which leads to reduction in motor nerve inhibition. This prevents the release of the GABA and glycine inhibitory neurotransmitters, causing unopposed muscle rigidity and spasms.

Alterations in sensation can also occur because of tetanus infection. Symptoms typically include allodynia and pain. Though it is unclear where tetanus affects sensory nerves, it is typically seen in the head and neck and may be related to toxin invasion of the trigeminal nerve.[1]

Clinical Characteristics

Tetanus remains a very rare disease, primarily affecting those who are unvaccinated and/or immunocompromised, with 17 cases reported in the United States in 2020 and 28 cases in 2021.[2] Vaccination has significantly decreased the incidence of tetanus infections, though there is still a large prevalence in countries which do not require vaccination. Throughout childhood, the CDC recommends four doses by age two years, with booster doses between ages 4 to 6 years and again at 11 to 12 years of age. After this age, boosters are recommended for the general population every ten years. After two doses, the vaccine produces antibody protection in 81-95% of patients, but this number rises to 100% after three doses.[3]

On average, symptoms tend to appear about ten days following spore entry, with longer times if the wound is further from the central nervous system. Disease severity is correlated to the speed at which symptoms develop – the more severe disease is seen with more rapid symptom development.[5] On average, tetanus infection lasts about six weeks – the first two weeks consist of disease progression and the remaining four weeks with symptom recovery.[4]

The clinical presentation of tetanus is categorized into four recognized forms: generalized, neonatal, localized (to a limb) and cephalic (localized to the head and neck).

Generalized Tetanus

The generalized form is the most common and presents as trismus (lockjaw) which is painful contraction of the temporal and masseter muscles, reducing the ability to open the mouth. When attempts are made to open the mouth, the patient may experience spasms which can cause the jaw to clench down further. Generalized tetanus also presents with muscle stiffness, followed by painful prolonged muscle spasms of the whole body. The strongest of the spasms occur in the extensor muscles or the back and neck, causing the characteristic opisthotonos (arching of the back due to rigidity of the extensor muscles).[5] Risus sardonicus is a noteworthy finding, which is sustained spasm of the facial muscles that induces a grimaced facial expression along with drooling. Close observation is necessary due to risk of pharyngeal and laryngeal spasms which can lead to airway obstruction and aspiration.

Rhabdomyolysis leading to acute kidney injury can be seen due to the severe, sustained muscle contractions and spasms.

Neonatal Tetanus

Neonatal tetanus can present similarly with generalized muscle involvement and opisthotonos but occurs in children less than one month of age and is due to exposure of the toxin through the umbilical cord. Respiratory failure can occur in generalized and neonatal tetanus, when there is involvement of the laryngeal and respiratory muscles; this may lead to aspiration, airway obstruction, and potentially intubation with mechanical ventilation.

Localized Tetanus

This is a very unusual clinical manifestation of tetanus. Symptoms of muscle rigidity and spasm only present around the site of injury. Typically, localized tetanus is seen in people with at least partial immunity. However, it can still progress to generalized tetanus.

Cephalic Tetanus

Patients with cephalic tetanus present with flaccid cranial nerve palsies and are commonly misdiagnosed as a stroke early in disease. Like localized tetanus, patients are also at risk for progression to generalized tetanus.

Acute Presentation

Tetanus is frequently diagnosed clinically. There are no confirmatory laboratory tests available and wound cultures are positive approximately 30% of the time.[5,6] At times, the wound will be fully healed by the time symptoms begin to appear, making diagnosis even more difficult.

Symptoms will frequently begin in the jaw with the classic "locked jaw," or trismus, secondary to masseter spasm. Over the next one to two days, symptoms of muscle rigidity and spasm will progress caudally and include dysphagia and opisthotonos. Some patients will also describe sensory alterations prior to muscle spasms. In addition to these generalized symptoms, autonomic disturbances will be present. These can include labile blood pressure, heart arrhythmias, hyperpyrexia, and sweating.[7]

Medical Management

It is recommended that the wound undergo debridement to remove and/or minimize the presence of any remaining tetanus spores.[7] This debridement should be done in an operating room with removal of damaged or dead tissue. Following debridement, routine wound care should be continued until fully healed.[7]

Treatment consists of both antitoxin administration and antibiotics. Tetanus antitoxin is given to neutralize any free toxin that has not been taken up by nerve terminals. This is given intramuscularly and should be administered as soon as tetanus is diagnosed. If tetanus antitoxin is not available, intravenous immunoglobulin (IVIg) is recommended to be given.[7] It is also important to provide tetanus vaccination during treatment, as infection does not result in immunity.[1,7] There are multiple studies underway evaluating the efficacy of intrathecal tetanus antitoxin compared to intramuscular administration. However, the intrathecal administration is not approved or recommended.[5]

Antibiotics are used to prevent additional proliferation of the *C tetani* bacterium at the wound site.[7] Penicillin, metronidazole, or doxycycline are recommended, with metronidazole being used most frequently.[1,7,8] Treatment is for seven to ten days, regardless of which antibiotic is chosen. Of note, there are some studies which state penicillin may exacerbate muscle spasms and lead to seizures. This is based on the ability of penicillin to inhibit GABA-A receptors and lead to decreased post-synaptic inhibitory signals, thereby amplifying the already affected inhibitory signaling process resulting in worsened spasms. A clear consensus on the use of penicillin has not been established.[1,7,8]

Once the toxin is taken up by the nerve terminals, it cannot be reached by the antitoxin or antibiotics. This can lead to continued symptoms progression despite adequate and complete treatment. Many patients require sedation and chemical paralysis to control the aggressive muscle spasms and autonomic dysfunction.

Autonomic Dysfunction

The tetanus toxin not only affects the motor system but can also cause autonomic instability. Autonomic dysfunction is typically seen in generalized and more severe tetanus. Elevated levels of epinephrine and norepinephrine in the blood stream occur due to tetanus toxin binding to sympathetic adrenergic neurons. The presence of autonomic symptoms also signals that the toxin has begun affecting the brain stem.[1] Symptoms include tachycardia, labile blood pressures intermixed with hypotension and bradycardia, sweating, dysrhythmias, fevers, and disturbances of bowel and bladder function. Early presentation of autonomic symptoms can be associated with higher change of mortality.[8] Early studies show efficacy with use of labetalol to counteract the adrenergic overdrive symptoms caused by tetanus. While it was effective in improving tachycardia and hypertension, the lability of both were not improved. Clonidine, an alpha 2 adrenergic agonist, is frequently used to treat autonomic dysfunction. It can be given orally, intradermally, or intravenously. Studies show that use of intravenous clonidine can help improve blood pressure fluctuations within a few days.[7] If patients require sedation, dexmedetomidine is recommended. This alpha-2 agonist has both sedative effects as well as autonomic effects.[7] It does not affect muscle spasm or rigidity.

Trismus

A common presenting symptom of generalized tetanus infection is trismus. This can lead not only to problems eating and swallowing but can also contribute to respiratory failure due to risk of aspiration.[1] It can also lead to dental health concerns due to inability to open the mouth for many weeks. Hassel recommends early consideration of botulinum toxin for management of trismus. Besides botulinum toxin injections, there are no other treatments for trismus and if present, providers must wait for the tetanus infection to take its course for the rigidity to resolve. As this can affect the ability to eat, alternative means of nutrition must be considered and initiated early in the acute phase.

Rehabilitation Medicine Management

There is no difference in the management strategies of adult vs pediatric tetanus infection. The only difference lies in dosing recommendations for medication administration.

Spasticity/Muscle Rigidity Management

Non-Pharmacological Management

The introduction of physical, occupational and speech therapy in cases of suspected tetanus is important to assist with early mobilization in the setting of rigidity and spasms. Early goals of

therapy include relieving pain, stretching tight muscles within available range, assisting with positioning, and attempting to prevent further physical deterioration. However, it is important to note that stretching and range of motion techniques are not successful during the acute rigid phase of a generalized tetanus infection. It is only when this phase resolves that physical modalities will become effective and important. At this time, therapists can utilize therapeutic massage, muscle strengthening, splinting/bracing, and serial casting to regain range of motion.[9] As the biggest risk of generalized tetanus infection is joint stiffness, it is important to start physical and occupational therapy as soon as possible. However, while early range of motion may be beneficial, it can also be an additional stimulus which may cause worsening spasms. Frequently therapy is deferred until the acute phase of the generalized infection has passed.[3]

Speech therapy is also utilized for dysphagia evaluation when trismus is present. Like the approach for physical and occupational therapy, therapists are limited in ability to treat patients until the rigidity and spasms resolve. Alternative nutrition means must be implemented until patients can safely consume nutrition by mouth.

It is also important to consider environmental factors that can provoke spasms. Spasm can be caused by loud noises, voices, turning on the lights, and frequent interventions for cares. It is recommended the room be quiet, with dim lighting, and limit the activity to limit the degree and frequency of muscle spasms..[10] In addition, consider using eye masks, ear plugs, and other external aids to reduce the stimuli the patient is experiencing.

As many patients will require prolonged immobilization in the intensive care setting, it is also important to monitor closely for the development of pressure wounds. Early use of specialty mattresses to help with pressure relief should be considered. Physical and occupational therapy can also assist with positioning techniques, especially in the initial period of rigidity.[3]

Pharmacologic Management

There are multiple medications used in the management of tetanus as listed in Table 1. It is extremely uncommon for only a single medication to be used. Most commonly, benzodiazepines, baclofen, and magnesium sulfate are used simultaneously. Due to severity of muscle spasms and need for high dosing of multiple medications, most patients requiring intubation for airway protection. In addition, muscle spasms can affect the chest and abdomen, making spontaneous respiration difficult and requiring intubation for adequate ventilation. Dosing recommendations are listed in Table 1.

Benzodiazepines

Benzodiazepines, especially diazepam, have become part of the standard treatment for the muscle spasms associated with tetanus infection.[1,7,8] This is likely because of the multiple effects of benzodiazepines – muscle relaxation, sedation, and anxiolysis. The most frequently used benzodiazepine is diazepam.[7] Benzodiazepines are GABA-A receptor agonists resulting in increased action of GABA on lower motor neurons.[1] Large doses of benzodiazepines are frequently required to control muscle spasms. Dosing is typically started intravenously while patients are sedated, sometimes in the form of a continuous benzodiazepine infusion, then migrated to enteral dosing when appropriate. As the patient's clinical status improves, the medication is weaned off as tolerated.

Baclofen

Like benzodiazepines, baclofen is also a GABA agonist, targeting the GABA-B receptors. It can be administered both enterally and intrathecally. However, enteral baclofen has poor penetration of the blood-brain barrier. As the effects of acute tetanus are mostly mediated by the central nervous system, the effectiveness of enteral baclofen is limited.[1,5,7,8] While there are no randomized controlled studies, multiple studies recommend the use of intrathecal baclofen during acute tetanus treatment. Intrathecal baclofen can be administered either through continuous infusion via catheter or intermittent injections.[5,7,8] There is no clear dosing recommendation for intrathecal baclofen, and most recommendations are for adult patients, making dosing for pediatric patients more difficult. Side effects of intrathecal baclofen administration include respiratory depression requiring mechanical ventilation and cardiovascular instability, therefore close monitoring in an intensive care setting is required.[7,8]

Dantrolene

While the previous medications have targeted the central nervous system, dantrolene works in the muscle. It binds to ryanodine receptors in the sarcoplasmic reticulum which release calcium ions from intracellular stores during excitation and contraction coupling in both cardiac in skeletal muscles. Dantrolene works by preventing calcium release, which in turn decreases muscle contraction.[7] A known adverse effect of dantrolene is hepatotoxicity. Special attention must be paid when utilizing dantrolene to treat spasticity/rigidity in patients with tetanus as they are at risk for rhabdomyolysis which can result in hepatic injury.

Botulinum toxin

Botulinum toxin (BoNT) is a neurotoxin produced by the bacterium Clostridium botulinum. There are several serotypes of BoNT all of which have a similar mechanism of action. When administered locally into striated muscle, BoNT causes a light chain protein to bind to SNARE proteins at the level of the neuromuscular junction which prevents the fusion of the vesicle, thereby inhibiting the release of the neurotransmitter, acetylcholine.[11] Acetylcholine is needed at the post-synaptic receptors of the neuromuscular junction to assist with the stepwise process to initiate muscle contraction.[12] The result of the BoNT mechanism of action is decreased muscle activity with the goal of muscle relaxation. BoNT is administered intramuscularly via an injection.

There are a limited number of case reports surrounding the use of BoNT for treating the symptoms of tetanus. Most commonly, BoNT has been used for the management of trismus. It has been suggested that use of BoNT should be considered in generalized tetanus when rigidity and/or spasms of certain muscle groups are impacting functional outcomes.[1] Multiple case studies have been done investigating the use of BoNT for muscle rigidity and spasticity related to acute tetanus infection. In all patients, the injections were

Table 1. Medications for Spasticity, Rigidity and Autonomic Dysfunction After Tetanus

Medication	Indication	Dosing	Side Effects
Diazepam	Muscle spasticity	PO: 0.12 to 0.8mg/kg/day divided every 6-8 hour IV: 0.04 to 0.3mg/kg/dose to maximum of 0.6mg/kg within 8 hours	Sedation, CNS depression
Baclofen	Muscle spasticity	Infants over 4 months and children under 2 years: 10-20mg per day divided every 8 hours; maximum 40mg daily	CNS effects (dizziness, drowsiness, sedation), urinary retention, nausea, constipation
		Children 2-7 years: 20-30mg per day divided every 8 hours; maximum 60mg daily	
		Children >8 years and adolescents: 30-40mg per day divided every 8 hours; maximum 120mg daily	
Magnesium sulfate	Muscle spasticity, autonomic dysfunction	Loading dose 40mg/kg over 30 minutes followed by -1.5g/hr if <45kg - 2g/hr if >45kg Goal Mg level 2-4 mmol/L	Hypocalcemia, magnesium toxicity which included arrhythmias, hypotension, respiratory, and CNS depression
Dantrolene	Muscle spasticity	Children under 5 years and <50kg: 0.5mg/kg/dose daily, increased to TID dosing then titrated up to 2mg/kg/dose TID; maximum 400mg/day	Hepatotoxicity with need for LFT monitoring, nausea, vomiting, muscle weakness
		Children and Adolescents >50kg: 25mg daily, increased to TID then titrated up to 100mg TID; maximum 400mg/day	
Botulinum toxin	Muscle spasticity	Approved for >2 years of age. - Upper extremity dosing: 3-6 units/kg divided among affected muscles - Lower extremity dosing: 4-8 units/kg divided among affected muscles - Maximum total dose 10 units/kg or 340 units total	Muscle weakness, spread to nearby muscles, antibody formation, problems swallowing, speaking or breathing
Labetalol	Autonomic dysfunction	0.25 - 1mg/min	Bradycardia, hypotension, bronchospasm, dizziness
Propranolol	Autonomic dysfunction	0.5 to 1mg/kg/day divided every 6 to 8 hours; max dose 4mg/kg/day	Bradycardia, hypotension, bronchospasm, dizziness
Vecuronium	Uncontrolled muscle spasms and rigidity	Loading dose 0.08-0.01mg/kg followed by infusion of 0.1mg/kg/hr	Minimal cardiovascular side effects. Prolonged use can lead to difficulty weaning from ventilator

well tolerated without negative side effects. In a study by Hassel, only one patient required repeat BoNT injections whereas the remainder of patients only required single injections.[1] It is important to note that BoNT is not approved for the treatment of tetanus, so this is an off-label usage.

While extremity BoNT will be guided based on clinical symptoms, injections for trismus typically target the masseter and temporalis muscles.[1] In addition, consideration can also be given to neck musculature that may be causing neck rigidity which can also affect feeding, swallowing, and breathing. Frequently targeted muscles are the trapezius, splenius capitis, levator scapulae, and sternocleidomastoid.[1]

Magnesium Sulfate

Magnesium works as a calcium antagonist that has multiple benefits in tetanus treatment. It can block the pre-synaptic release of acetylcholine which prevents continued muscle contraction.[1]

In addition, magnesium is also helpful in treating the autonomic dysfunction that can occur by leading to vasodilation and prevention of catecholamine release.[1,7] Careful monitoring is required to ensure magnesium toxicity does not occur with frequent serum level testing and monitoring of serum calcium levels. Some studies have shown benefits with treatment of both diazepam and magnesium.[4,5]

Beta Blockade

Beta blockers are also used for autonomic dysfunction. Labetalol is frequently used as an infusion as it blocks both alpha and beta receptors. Propranolol is also used as it is quick acting and can control tachycardia, hypertension, and supraventricular tachycardia.[3]

Paralytics

Unfortunately, the above medications are not always sufficient in controlling muscle spasms. This can lead to pressure wound formation due to posturing or difficult ventilating in the setting of chest and trunk spasms. In these instances, neuromuscular blockade

through paralytics is indicated. Vecuronium is the preferred agent due to its minimal action on the autonomic nervous system. However, it is very short acting, so a continuous infusion is required.[3] Patients receiving paralytics must be intubated and in the intensive care unit as they will need ventilatory support.

Nutrition Management

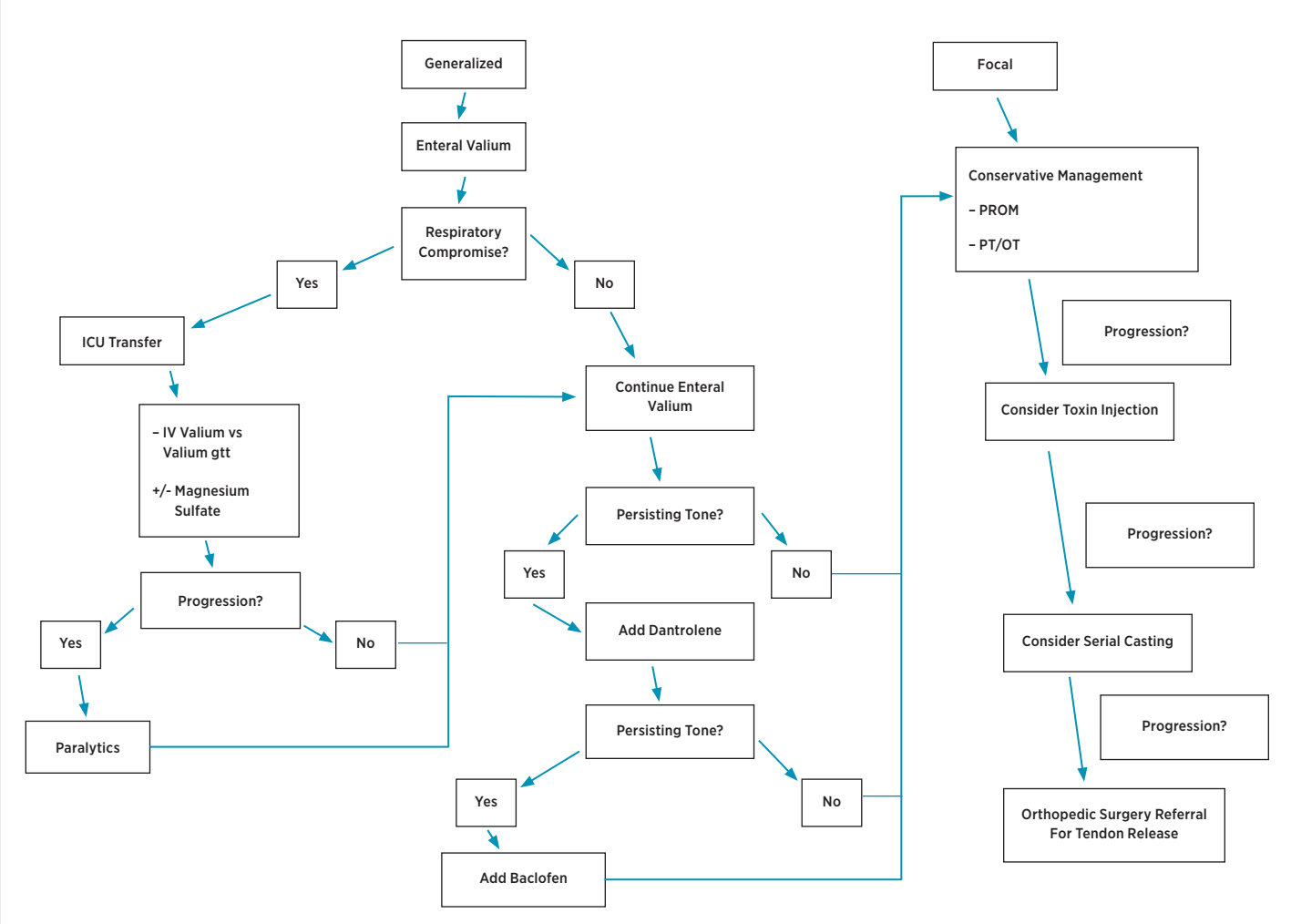
With trismus and dysphagia being common presenting symptoms in generalized tetanus, achieving adequate nutrition by mouth is not typically possible. In addition, due to the degree of muscle spasms, most patients have very high caloric needs during acute infection. Enteral nutrition, typically via nasogastric tube, is preferred 3. Patients are also at risk of impaired gastrointestinal motility due to spasms and side effects from sedative medications, so close monitoring for development of an ileus is recommended. If enteral feedings are not tolerated patients should be transitioned to parenteral nutrition. Recommended caloric intake depends on patient age and weight, and nutrition should be consulted to determine a child's specific needs. Rough estimates of daily caloric needs are listed in Table 2.[13]

Table 2: Nutritional Requirements After Tetanus by Age

Age	Caloric Needs in kcal/kg/day
Under one year	100
One to three years	80
Four to five years	70
Six to eight years	60-65
Age 9 and older	35-45

UPMC Children's Hospital of Pittsburgh Tetanus Clinical Pathway for Rigidity Management

It is hard to generalize the treatment of rigidity in acute tetanus as the severity varies greatly and will dictate which treatments are utilized. At UPMC Children's Hospital of Pittsburgh, we have a general pathway that we follow when we are seeing children with acute tetanus infection, which is outlined below in the graph below. This pathway was derived with pediatric critical care medicine, pediatric rehabilitation medicine, and therapy services.



Clinical Vignette Summary

At the time of initial PRM consultation, the patient was noted to have persistent trismus with open mouth posture, appropriate/normal muscle tone to the bilateral upper extremities, decreased passive range of motion (PROM) and active range of motion (AROM) of the bilateral lower extremities most notable for resting in bilateral ankle plantarflexion, and spasticity to the bilateral lower extremities. Specifically, he was noted to have an MAS 2 to the left quadriceps, hamstring, and plantar flexors; MAS 3 to the right quadriceps and hamstring; MAS 4 to the right plantar flexors. The PROM/AROM of his bilateral plantar flexors was limited to -35 degrees on the right and -20 degrees on the left with knee flexion and extension. Dantrolene was started for spasticity/rigidity management. He was admitted to the UPMC Children's Hospital Rehabilitation Unit (CHRU) for acute inpatient rehabilitation. At the time of admission, the patient was ambulating with various levels of assist (moderate vs maximum assistance) with the use of a wheeled walker with a hip hike compensatory strategy to help with foot clearance due to toe catching in setting of plantarflexion positioning. During his CHRU course, his overall spasticity and rigidity improved. He was successfully weaned off diazepam and was maintained on dantrolene 25mg three times daily (0.7mg/kg/dose). His symptoms of dysautonomia resolved and he successfully completed a clonidine wean.

Early in his CHRU course, he received anatomic guided onabotulinumtoxinA to the bilateral gastrocnemius (75 units each; total dose 150 units) followed by a trial of serial casting to the bilateral ankles which occurred over the course of one week. Following the combination of onabotulinumtoxinA and serial casting, the patient was noted to have improved PROM/AROM of the bilateral plantar flexors measured as lacking ~25 degrees on the right and neutral positioning on the left. He was ambulating with supervision using a wheeled walker.

The patient was seen for follow-up ~ 4 weeks post-discharge from the CHRU and ~ 6 weeks post-neurotoxin injections. At the time of follow-up evaluation, he was noted to have PROM/AROM to at least neutral to the bilateral ankles. His strength was age appropriate throughout all extremities. The patient was ambulating independently without any compensatory gait strategies and/or use of assistive devices. At that time, a dantrolene wean schedule was established and completed as an outpatient. The patient was reportedly back at his pre-hospitalization baseline functional status.

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