Tetanus in developing countries: a case series and review

Série de cas et synthèse: le tétanos dans les pays en voie de développement

Kara Gibson, MD · J. Bonaventure Uwineza, MD ·
Willy Kiviri, MD · Joel Parlow, MD

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Abstract

Purpose Few anesthesiologists have expertise in the diagnosis and treatment of tetanus, a disease that remains prevalent in developing countries. We report on a series of four cases of tetanus cases recently encountered in Rwanda. We review the clinical epidemiology, pathophysiology, diagnosis and the treatment of tetanus, and provide implications for anesthesiologists and critical care physicians.

Clinical features We report four cases, two involving adults who were inadequately vaccinated and experienced injuries, and two involving neonates, both of whom underwent umbilical cord transection using unsterilized equipment. All patients required tracheal intubation, and were mechanically ventilated when equipment was available. One adult and one neonate succumbed to the disease. These cases highlight the difficulties of diagnosis and management of complicated diseases in the resource-challenged health care setting of developing countries.

Conclusions The differential diagnosis of tetanus may be confusing, and survival depends on the rapidity of treatment with antitoxin, as well as adequate supportive care. High doses of sedatives and muscle relaxants, as well as prolonged mechanical ventilation, are usually necessary. Mortality remains high, usually resulting from late respiratory failure and cardiovascular collapse, associated with

autonomic instability. Anesthesiologists and critical care physicians have an important role to play in the management of these patients. Increased involvement in humanitarian health organizations, immigration from developing countries, and emergence of high risk groups in developed countries will likely result in more exposure of anesthesiologists to the complexities of this disease.

Résumé

Objectif Très peu d'anesthésiologistes sont experts du diagnostic et du traitement du tétanos, une pathologie qui demeure prévalente dans les pays en voie de développement. Nous rapportons une série de quatre cas de tétanos survenus récemment au Rwanda. Nous passons en revue l'épidémiologie clinique, la physiopathologie, le diagnostic et le traitement du tétanos, et proposons des pistes intéressantes pour les anesthésiologistes et les médecins en soins critiques.

Éléments cliniques Nous rapportons quatre cas dont deux impliquent des adultes mal vaccinés et qui ont subi des blessures, et deux concernent des nouveau-nés, tous deux ayant subi une coupe transversale du cordon ombilical à l'aide d'instruments non stérilisés. Tous les patients ont nécessité une intubation trachéale et ont été ventilés mécaniquement lorsque le matériel était disponible. Ces cas soulignent les difficultés rencontrées lors du diagnostic et de la prise en charge de pathologies complexes dans le contexte des soins de santé manquant de ressources des pays en voie de développement.

Conclusions Le diagnostic différentiel du tétanos peut porter à confusion, et la survie dépend de la rapidité du traitement avec de l'antitoxine ainsi que de soins d'accompagnement adaptés. En général, des doses élevées de sédatifs et de curares ainsi qu'une ventilation mécanique prolongée sont nécessaires. La mortalité demeure

K. Gibson, MD · J. Parlow, MD (✉)
Department of Anesthesiology, Queen's University, Kingston
General Hospital, 76 Stuart Street, Kingston,
ON K7L 2V7, Canada
e-mail: parlowj@kgh.kari.net

J. Bonaventure Uwineza, MD · W. Kiviri, MD
Département d'Anesthésie et Réanimation, Centre Hospitalier
Universitaire de Kigali, Kigali, Rwanda

élevée, en général causée par une insuffisance respiratoire tardive et d'une défaillance cardiovasculaire combinées à une instabilité du système nerveux autonome. Les anesthésiologistes et les médecins en soins critiques ont un rôle important à jouer dans la prise en charge de ces patients. Un engagement accru dans les organisations sanitaires humanitaires, l'immigration des pays en voie de développement et l'émergence de groupes à haut risque dans les pays développés auront probablement pour résultat une plus grande exposition des anesthésiologistes aux éléments complexes de cette pathologie.

The treatment of tetanus has many implications for anesthesiologists and critical care physicians, but most physicians in developed countries lack experience in dealing with such cases. With developed nations progressively more involved in the medical aid programs in developing countries, and with increased immigration and emerging risk groups in developed countries, physicians may increasingly be called upon to diagnose and treat this complex disease.

Since 2006, the Canadian Anesthesiologists' Society International Education Foundation (CAS-IEF), in conjunction with the American Society of Anesthesiologists, has made visiting faculty available as teachers for local anesthesiology residents and allied personnel in Rwanda. We recently participated in the CAS-IEF program in Rwanda and, during the month of February, 2008, encountered four new cases of tetanus presenting to the Intensive Care Unit of the Centre Hospitalier Universitaire de Kigali (CHUK), Rwanda's largest public hospital. With approval of the institutional ethics committee, the *Comité de Recherche Scientifique au CHUK*, we present a summary of these cases and a review of the pathophysiology, treatment options, and anesthetic considerations of tetanus.

Case series

Case 1

A 28-year-old man who was involved in a motorcycle accident presented the same day to a local health centre with a soft tissue wound of his left leg. The wound was cleaned and bandaged, but no tetanus toxoid was given. Five days later, he returned to the clinic complaining of fever, arthralgias, and myalgias. A diagnosis of malaria was presumed (endemic in this area), and antimalarial drugs were prescribed. Two days following this visit, he again returned to the clinic, having developed neck pain, difficulty opening his jaw, and swallowing. The patient was transferred to a district hospital 7 days after his injury.

At the district hospital, the diagnosis of tetanus was made based on the patient's history of trauma, unknown vaccination coverage, cervical rigidity, and trismus. At this time, equine antitetanus immunoglobulin was administered intramuscularly. Since the district hospital did not have diazepam to treat muscular spasms, the patient was referred the same day to CHUK, the national referral hospital in Kigali.

On arrival at CHUK, the patient was breathing spontaneously but requiring oxygen. He was alert and his vital signs were stable. Pertinent physical signs included trismus, opisthotonus, and an oozing leg wound. He was admitted to the intensive care unit and treated with metronidazole for wound infection and diazepam titrated up to $16 \text{ mg} \cdot \text{h}^{-1}$ *iv*. Late on the evening of Day 3 of his illness, the patient suffered multiple generalized paroxysms that were treated with additional boluses of diazepam. Morphine infusion was commenced at $1 \text{ mg} \cdot \text{h}^{-1}$. Vital signs remained stable. Five hours later, generalized contractures were noted, ventilation was deteriorating, and the patient's trachea was intubated to facilitate mechanical ventilation. Sedation and muscle relaxation consisted of morphine $8 \text{ mg} \cdot \text{h}^{-1}$, diazepam $20 \text{ mg} \cdot \text{h}^{-1}$, and vecuronium $0.8 \text{ mg} \cdot \text{h}^{-1}$ *iv*. Daily enoxaparin was given for deep vein thrombosis prophylaxis. The following day, the patient developed a fever and ampicillin was started. Vecuronium was replaced with pancuronium $1.8 \text{ mg} \cdot \text{h}^{-1}$ and magnesium sulfate $80 \text{ mg} \cdot \text{h}^{-1}$ was infused. On Day 5, sodium thiopentone was added at a dose of $100 \text{ mg} \cdot \text{h}^{-1}$ and doses of diazepam and morphine were reduced. On Day 6, the patient's temperature rose to 40°C ; lumbar puncture was performed, which ruled out meningitis, and a blood smear for malaria proved negative. The patient received a tracheostomy on Day 8. High levels of positive end-expiratory pressure and inspired oxygen fraction of 0.8 were required to maintain adequate oxygen saturation in the immediate postoperative period. On Day 9, left-sided pneumonia was diagnosed clinically and by chest radiography and was treated with ceftazidime. No organism was isolated from bronchial secretions. By Day 16, oxygenation was further impaired, bilateral rales were present, and chest radiography showed bilateral airspace infiltrates. The patient was hypotensive and presumed to be in septic shock secondary to ventilator-acquired pneumonia. Late that evening, 21 days after injury and 16 days after onset of illness, the patient died of respiratory failure.

Case 2

A 30-year-old farmer suffered a machete injury to his left index finger while working in the field. Ten days after injury, he first consulted with his local health clinic complaining of difficulty chewing and swallowing. The

clinicians quickly decided to refer him to the district hospital, where, in turn, he was transferred to CHUK.

On admission to CHUK, he was alert and oxygenating well on room air, but was manifesting all the typical signs of tetanus: generalized muscle spasms, opisthotonus, trismus, risus sardonicus facies, as well as nuchal rigidity, rigid abdomen, and a small healing wound on the index finger. The diagnosis of tetanus was made at this time, Day 1 of his illness, as was the diagnosis of malaria. The patient had no known history of having received a tetanus vaccination and was negative for antibodies to human immunodeficiency virus (HIV). Tetanus treatment included equine antitetanus immunoglobulin 3000 IU IM, metronidazole, diazepam 10 mg · h⁻¹, oxygen by nasal cannula, and admission to the intensive care unit. Phenobarbital 50 mg *iv* qid was initiated for persistent paroxysms. Intravenous and nebulized atropine was administered for bronchial secretions. On Day 10 of his illness, pneumonia was diagnosed, based on a productive cough, fever of 38.5°C, and changes on chest radiograph. This was treated with ceftriaxone 2 g bid and gentamicin 80 mg bid. On Day 12 of the onset of his illness, the patient was intubated for respiratory distress in the face of persistent paroxysms of muscular spasm. Sedation and relaxation consisted of diazepam and sodium thiopentone 40 mg · h⁻¹, morphine boluses, and vecuronium. The patient's trachea was extubated on Day 18. He was discharged from hospital 24 days after admission, his only deficit being a flaccid left hand. He has returned to work with his community to promote awareness of the importance of tetanus vaccination.

Case 3

A 10-week-old male infant was admitted to the intensive care unit at CHUK. The infant was born at term at home with a traditional birth attendant. The 19-year-old mother had only once been medically evaluated antenatally and had received one dose of tetanus vaccine. The umbilical cord had been cut with a previously used razor blade with no sterile precautions taken. No perinatal problems were noted. The family visited the district hospital shortly after the birth for a well-baby check-up; however, the infant's vaccinations were delayed by 1 week due to refrigeration problems. Six weeks after birth, the infant developed episodic convulsions, spasms of his lower extremities, increased oral secretions, and cervical rigidity. The patient was not admitted to hospital until 1 week later, at which time he presented with generalized nonfebrile convulsions, muscular rigidity and spasms, transient apnea, and reduced reflexes. During a 3-week course in the district hospital for an undetermined illness, the infant received oxygen by mask, diazepam, and hydrocortisone. Lumbar puncture was performed during the course in hospital and reported as

"blood-tinged." Fever prompted a blood smear for malaria, which was positive, and antimalarial drugs were started.

On Day 28 after onset of illness, the infant was eventually transferred late in his course to CHUK for suspected hemorrhagic meningitis, malaria, and possible tetanus. Upon admission to CHUK, he received his first dose of equine antitetanus immunoglobulin 500 IU *im*. The infant also received rectal diazepam 0.5 mg · kg⁻¹, phenobarbital infusion 20 mg · d, dexamethasone, ceftriaxone, metronidazole, and oxygen by face mask. The infant was fed by gastric tube, and his trachea was intubated for airway protection following an episode of emesis after feeding. Ventilation was impaired due to muscle spasms and opisthotonus; however, there was no neonatal ventilator available at this time in the intensive care unit. The infant maintained spontaneous respiration via endotracheal tube for 2 days. His trachea was extubated on Day 30 after the convulsions and spasms had regressed. The infant was discharged 5 weeks after admission to CHUK and 9 weeks after onset of illness.

Case 4

A male infant was diagnosed with tetanus only 4 days after birth. This infant was a second child born at home to an HIV negative mother who had only been seen once prenatally and had received a single dose of antitetanus immunoglobulin at 8 months' gestation. After delivery, the umbilical cord was cut with unsterilized hairstyling scissors. At 4 days of age, the infant presented to a local hospital with generalized muscle spasms and was treated with diazepam and metronidazole. No antitetanus immunoglobulin was given. After making little improvement, he was transferred to CHUK on Day 10 after onset of illness.

On arrival to CHUK on Day 10, the infant was opisthotonic; he also had trismus and excessive oral secretions. There was no bulging of fontanelles. The umbilical stump appeared infected. Intensive care admission and treatment included oxygen by face mask, intramuscular equine antitetanus immune globulin 500 IU *im*, cefotaxime, metronidazole, diazepam 0.4 mg · h, acetaminophen, magnesium sulfate, and calcium gluconate. Persistent muscle spasms necessitated increased diazepam doses as well as sodium thiopentone. He was nourished with nasogastric feeds. The infant remained agitated, and because he had difficulty managing his copious secretions, the infant was tracheally intubated but not mechanically ventilated. The intubation was difficult in the absence of muscle relaxants, which were avoided in order to maintain spontaneous respiration. Continued problems with endotracheal tube obstruction due to secretions necessitated tube replacement. Four days following his intubation, the infant became increasingly hypoxemic and subsequently bradycardic. Cardiac arrest ensued, and no epinephrine was

available for resuscitation. The child expired following failed attempts at improving oxygenation.

Discussion

Tetanus is a rare condition in the western world, primarily due to widespread vaccination programs from infancy to adulthood. In many developing nations, tetanus, as with other preventable diseases, is still common. This disease has many implications for anesthesiologists and critical care physicians.

Pathophysiology

Tetanus toxin, or tetanospasmin, is released from *Clostridium tetani* spores that live everywhere in the soil. It is one of the most potent toxins in nature—240 g is estimated to be sufficient to kill the world's population.¹ *C. tetani* spores usually enter the tissue through a penetrating contaminated wound, and after a period of anaerobic incubation, they become bacilli that release tetanus toxin. The toxin enters peripheral neurons and travels retrograde up axons to the central nervous system. It can enter motor, sensory, and autonomic neurons, although radiolabelled assays have shown a predilection for inhibitory neurons. Most of the clinical disease results from motor and autonomic inhibition. Tetanospasmin is a metalloprotease substance which acts at the presynaptic membrane to cleave synaptobrevin, a protein that allows fusion of neurotransmitter vesicles to nerve membranes. When this fusion process is prevented, neurotransmitters are not released into the synapse and neurotransmission is blocked. Centrally, transmission along the inhibitory gamma-amino butyric acid (GABA) and glycinergic neurons is interrupted, and at the level of the spinal cord, inhibitory interneurons are blocked.²

It is important to recognize that tetanus is not an infection, and therefore patients do not usually experience symptoms of the disease until the toxin is disseminated and reaches the interneurons.² Early treatment with immune globulin is critical, because it binds free toxin. However, it does not treat the effects of toxin protected within the neuron or cell body. Treatment of the effects of toxin already within the nervous system is purely supportive, as will be described further. Clinically, the effect of the toxin on the neuron lasts approximately 4–6 weeks and may be irreversible until the re-growth of a new nerve terminal; however, the mechanism of functional recovery is not clear.^{2,3}

Epidemiology and prevention

Adult and neonatal tetanus are still common in many developing countries. Estimates from 2002 suggest that

between 213,000 and 293,000 deaths from tetanus occur worldwide each year, including 180,000 infant deaths from neonatal tetanus.⁴ While still a high overall mortality, rates of neonatal tetanus have decreased from the 787,000 deaths reported in 1988.⁴ Accurate estimates of incidence are difficult to obtain for logistical reasons. In certain regions of some developing countries, fewer than 10% of cases have been reported.⁴ In contrast, an average of four cases of tetanus per year are reported in Canada, 12–15 cases per year in the United Kingdom, and 50–70 cases per year in the United States.⁵

In the developing world, mortality from tetanus exceeds 50%, with most deaths being from early, acute respiratory failure.⁶ In one review, a decrease from 44% to 15% in overall tetanus mortality was observed after the introduction of intensive care management and ventilators, reflecting the effectiveness of these resources in the management of tetanus.⁶ In this setting, the leading causes of death from tetanus were cardiovascular (40%) and pneumonia (15%), rather than acute respiratory failure. In developed countries, mortality among high-risk groups, such as the elderly, is still as high as 52%.^{1,7} Myocardial infarction may be a consequence of autonomic dysfunction and likely contributes to the increased mortality in the elderly population.⁶

Effective immunization requires five encounters with the health care system by the age of 15 years, followed by booster immunizations every 10 years.⁵ After a five-dose immunization schedule, usually completed before young adulthood, the duration of protection may last as long as 25 years. Regular access to the health care system is requisite to maintaining protective immune status against tetanus. Such a rigorous immunization schedule continues to be a challenge in developing countries where health care systems and physicians are already stretched beyond resources. Other co-morbid conditions present obstacles to achieving tetanus immunity. The HIV has been shown to decrease the immune response to tetanus immunization. In addition, malaria reduces placental transfer of antibodies to the fetus.⁸ Even in developed countries, such as the United States and the United Kingdom, serological surveys have shown that 49–66% of people over 60 years of age have inadequate immunity. Indeed, 70% of tetanus cases and 80% of deaths in these countries occur in people over 50 years of age.^{4,7} Recently, 24 cases of tetanus in the United Kingdom were reported among injection drug users, with intramuscular and subcutaneous injections leading to an especially high risk for developing the disease.¹ Most of these patients had either no record or an incomplete record of immunization. A recent serologic survey to determine the susceptibility of Canadians to tetanus identified the following risk factors: increasing age, birth outside of Canada, and incomplete or unknown immunization status.

Other epidemiologic studies have identified specific at-risk populations within Canada, including:

- (a) The elderly, who may not have been vaccinated in school before the immunization program began in 1940.^{9,10}
- (b) Birth outside of Canada or those from countries without reliable immunization programs (immigration medical exams do not require tetanus immunization).^{9,10}
- (c) Children from low income households.¹¹
- (d) First Nations children living on reserves.¹²
- (e) Young offenders.¹³
- (f) Those without immunization records or unknown immunization status.¹⁰
- (g) Immune-compromised patients, as they may not mount a full response to immunization. This includes patients with HIV,^{8,9} or those receiving immune depressant drugs, since only 50% of patients receiving chemotherapy for leukemia or lymphoma retain immunity to tetanus, despite being fully immunized.⁹

In Canada, women should not require additional tetanus immunizations during pregnancy if they have received regular immunizations.⁹

Natural history

Tetanus has four general clinical presentations: local, cephalic, generalized, and neonatal. Local tetanus involves only the site of injury but is often unrecognized until it becomes generalized. Cephalic tetanus is a form of local tetanus originating from head injuries or infections, such as otitis media. Generalized tetanus is the most common form and represents 80% of cases.⁷ Neonatal tetanus is a form of generalized tetanus that usually occurs within 28 days of birth. It also carries a very high mortality and accounts for 50% of deaths from tetanus.⁴ Neonatal tetanus is acquired from contamination of the umbilical stump, and protection is conferred through maternal transfer of antibodies to the fetus.^{3,4,8}

The natural course of the disease typically begins with a wound contaminated by soil, manure, or rusted metal. Puncture injuries are the most common method of entry, but tetanus has been reported after fractures, burns, animal scratches, otitis media, contaminated surgical wounds involving the gastrointestinal tract or abortions, as well as umbilical cord contamination.^{3,4,7} In approximately 20% of cases, no entry site can be found.^{3,7} The *incubation period*, defined as the time from injury to first symptom, can range from one to 60 days. This is followed by the *onset period* (time to first spasm), which ranges from 1 to 7 days.³ The first symptoms are commonly neck and jaw stiffness. Spasms are predominant in the first week of illness and continue for up to 3 weeks, while rigidity can persist up to

4–8 weeks. Autonomic instability peaks in the second week and usually subsides after the third week if the patient survives the sequelae of the hemodynamic derangements.³

The beginning of symptoms heralds the widespread dissemination of tetanus toxin throughout the nervous system. Progression of disease moves predictably caudad until the disease is generalized. Early involvement of the head and neck manifest as trismus from masseter spasm, and “risus sardonicus,” the well-known facies of tetanus, originates from spasm of facial muscles. Rigidity of the chest wall and abdominal muscles and diaphragmatic paralysis or spasm can cause respiratory failure from hypoventilation. Paroxysms involving the pharynx and larynx can cause acute airway obstruction. Generalized paroxysms appear similar to epileptic convulsions, but without loss of consciousness, and long bone fracture and tendon rupture have been reported. Truncal spasm locks the patient in the classical position of opisthotonus. Renal failure from rhabdomyolysis has been reported from the ongoing muscle rigidity.^{1,3,7} Severe tetanus is marked by clinically significant autonomic instability that has been compared to the hemodynamic changes of a pheochromocytoma.^{1,7} This period is extremely labile and is characterized by malignant levels of hypertension and tachycardia, followed by profound hypotension and bradycardia. In the past, acute respiratory failure was the leading cause of death from tetanus. With improved ventilatory management and intensive care, sudden cardiac arrest, often preceded by bradycardia, is now a primary cause of death from tetanus.⁶ Autonomic dysfunction also includes gastric stasis, ileus, diarrhea, bronchial secretions, salivation, pyrexia, and diaphoresis. Other serious sequelae of severe tetanus include pulmonary edema, myocardial dysfunction, acute respiratory distress syndrome, pneumonia, sepsis, pulmonary embolus, gastrointestinal bleeding, and poor nutritional status.^{6,7}

Several factors are predictive of a more severe course of tetanus and increased mortality. An incubation period of <5 days carries this poor prognosis as does an onset time of <48 h.^{3,14} Extremes of age, lack of previous immunity, and early autonomic instability also correlate with more severe disease and increased mortality.^{1,3,4,14}

Diagnostic dilemmas in the developing world

Ultimately, the diagnosis of tetanus is clinical, based on a compatible history and typical physical findings of rigidity, spasms, and trismus. Prompt diagnosis and treatment of tetanus improves the prognosis.¹⁴ A common reason for delayed treatment is the often confusing differential diagnosis and lack of specific confirmatory laboratory tests.³ The differential diagnosis for tetanus includes temporomandibular joint disease, alveolar abscess, meningitis,

cerebral malaria, encephalitis, subarachnoid hemorrhage, epilepsy, hypocalcemia, drug-induced movement disorders, stiff man syndrome, drug withdrawal, rabies, and strychnine poisoning.^{1,3,4} As was seen in the patients included in our case series, malaria is so prevalent in many developing countries that its presumptive diagnosis often results in a critical delay in the treatment of early tetanus.

Management of established tetanus

In general, management goals in tetanus have remained similar over the last half century, although drugs and therapeutic interventions have improved. Historically, anesthesiologists have been involved in tetanus management for their expertise in pharmacologic muscle relaxation, tracheal intubation, and mechanical ventilation.¹⁵ Following their experience in the poliomyelitis epidemics in Copenhagen in 1952, Ibsen and Lassen applied new muscle relaxation techniques with mechanical ventilation to tetanus patients.¹⁵ Prior to this, hypoventilatory respiratory failure from muscle paroxysms was the major cause of death from tetanus.⁵ Baker recognized the autonomic instability which develops in tetanus as early as 1942.¹⁶ However, until intensive care facilities and mechanical ventilation became available in areas of the world still encountering tetanus, patients did not typically survive far enough into the course of their disease to experience the severity and consequences of the hemodynamic derangements.⁶ This has expanded the role of anesthesiologists and intensive care specialists to include hemodynamic monitoring and pharmacologic manipulation of the autonomic nervous system. The management of tetanus in the intensive care setting focuses on three areas: (a) control of the toxin, (b) treating spasms, and (c) hemodynamic management. For lack of an evidence-based body of literature, treatment strategies are still primarily guided by case reports.

Reduction of active toxin

Control of the toxin involves reducing the load of the clostridium bacteria and is accomplished by aerating and debriding the wound to reduce anaerobic conditions that favor growth of the clostridium bacilli. Antibiotics are administered, with metronidazole being the drug of first choice. The use of penicillin has been controversial, and some trials have shown increased mortality when it is chosen over metronidazole.¹ This is thought to be due to the action of the GABA-like structure of penicillin that has an excitatory effect on the CNS in large doses and may act synergistically with tetanospasmin to cause hyperexcitability and convulsions.¹⁷

Treatment of circulating tetanus toxin is with human tetanus immunoglobulin (HTIG) or equine antiserum. This does not affect the toxin already present in neurons. The half-life of HTIG is 23 days, and recommendations for dosing intervals vary. While some authorities suggest that repeat dosing should not be necessary, others advise repeated administration if symptoms reappear after an initial response to immune globulin, presumably due to new release of toxin from remaining bacilli.⁷ The optimal route and dose are also debated. A recent meta-analysis shows significant mortality benefits with high dose (1000–1500 U) intrathecal HTIG or equine antiserum in adults and neonates compared to the intramuscular route (RR 0.71; CI 0.62–0.81, $P = 0.037$), with a greater improvement seen in adults.¹⁸ Tetanus toxoid immunization should always be given for long-term immunity, as neither the disease itself nor HTIG confer immunity. This can be administered during treatment for acute tetanus but should be given at a different site from HTIG to avoid interaction. Anaphylactic reactions to equine antitoxin occur in approximately 20% of cases, much higher than that for HTIG.¹⁷ However, the equine antiserum is often more available in developing countries.

Management of muscle spasm and ventilation

Initial management of muscle spasms involves sedation and a dark, quiet room. Numerous approaches are reported in the literature to relieving spasms, including benzodiazepines, barbiturates, anticonvulsants, narcotics, baclofen, dantrolene,³ and propofol.⁸ Pretreatment with sedatives and analgesics may be necessary prior to nursing care and procedures to avoid triggering paroxysms. Benzodiazepines are often used as first-line treatment. Baclofen has been shown in a few case series to completely relieve spasms when given via the intrathecal route but carries a significant risk of respiratory depression.⁷ The use of magnesium as a muscle relaxant has been studied by Thwaites *et al.*¹⁹ in a well-designed randomized controlled trial. The authors did not find a reduction in the need for mechanical ventilation in patients with tracheostomies with an infusion of magnesium to maintain serum concentrations at 2–4 mmol · L. On the other hand, magnesium reduced the requirement for medications used for muscle spasm and cardiovascular instability. No clinically significant hypocalcemia or impairment in ventilation was observed in any of the 98 patients receiving magnesium infusion.

The anesthesiologist may be consulted for management of emergent acute respiratory failure from laryngospasm or subacute respiratory failure. The diaphragm and the laryngeal and pharyngeal muscles are all affected, and in combination with the profuse bronchial and oral secretions

seen in tetanus, management of an unsecured airway is difficult. Accompanied by increased abdominal pressures and gastrointestinal stasis, even the awake patient is at increased risk of aspiration, which is a common complication.⁷ It should be noted that the literature does not report trismus to be a problem during tracheal intubation after neuromuscular relaxation. The response to depolarizing and non-depolarizing neuromuscular blockade is normal in tetanus,²⁰ although use of depolarizing agents, such as succinylcholine, should be carefully considered. Repeated administration of intramuscular succinylcholine without complication has been documented for the treatment of tetanic contractures.²¹ However, there are at least two reports of hyperkalemic cardiac arrest after succinylcholine administration late in the course of tetanus.²² Pancuronium carries the theoretical risk of increased adrenergic activity but has been shown not to increase complications when compared to other agents.⁷ Myopathy of critical illness has not specifically been documented in the literature, but, as with other long-term outcomes after surviving tetanus, the paucity of data should not preclude its consideration. Hypoxemia is a common problem, even in the intubated patient, because of a restrictive defect from chest wall rigidity leading to atelectasis and increased bronchial secretions obstructing the airways.⁷ Hypoxemia from ventilation-perfusion mismatch may occur without chest radiograph abnormalities.⁷ Prolonged ventilation puts the patient at increased risk of pneumonia, which often complicates the course of severe tetanus, as does sepsis and Acute Respiratory Distress Syndrome.^{6,7} In developing countries, tracheostomy is often performed for airway protection. Where access to mechanical ventilation is limited, efforts are made to maintain spontaneous respiration for as long as possible.

Management of circulatory disturbances

Autonomic instability constitutes one of the most challenging components of managing tetanus and is a common cause of death later in the disease.²³ Unfortunately, there has been little research addressing this autonomic syndrome, and the optimal treatment remains unclear.²³ “Autonomic storms,” consisting of episodic and extreme hypertension and tachycardia, often occur without a precipitating event. The resulting hyperdynamic circulation seems primarily to be driven by elevated basal levels of norepinephrine,²³ with spikes in epinephrine levels during autonomic crises.²⁴ Epinephrine levels of 100 times normal have been measured,²³ resembling levels occurring with pheochromocytoma.^{7,23} It has been suggested that acetylcholine excess is also involved in the autonomic dysregulation.²⁵ Lesions of the vagal nuclei in the brainstem have been reported and may contribute to the

profound vagal tone often seen in tetanus.³ Autonomic storms are often followed by severe, resistant hypotension, bradycardia, and even asystole. The hemodynamic changes are a result of massive fluctuations in the systemic vascular resistance index (SVRI), with little change in the cardiac index. Periods of increased SVRI coincide with intense muscular spasm, while low to normal SVRI coincides with relaxation. Similarly, central venous pressure increases during muscle spasm and decreases during muscle relaxation. Fluid challenges of 2 L during hypotensive episodes result in a very transient increase in cardiac index and filling pressures. The stroke volume index and the cardiac index are raised throughout the course of tetanus, unless complicated by acute respiratory distress syndrome or sepsis.²⁴ However, a direct depressant effect of the tetanus toxin on the myocardium has been postulated.⁷ Oxygen extraction remains normal, so increased delivery of oxygen is required by the hypermetabolic peripheral tissues.^{17,24}

Hypertensive crises have been treated with a variety of classes of drugs. Alpha-adrenergic antagonists, such as phentolamine, and mixed adrenergic antagonists, such as labetalol, have been used with the disadvantage of a risk of profound hypotension between crises.⁷ Propranolol has been associated with pulmonary edema and sudden death, possibly from unopposed alpha-adrenergic activity.²³ The cardioselective beta adrenergic antagonist, esmolol, is quickly titratable and produces adequate cardiovascular control, although arterial catecholamine levels remain elevated.⁷ The alpha-2 agonist, clonidine, has been used with variable success.^{7,23} Epidural and spinal bupivacaine have resulted in improved cardiovascular stability but required vasopressor support.⁷ Calcium channel blockers have been used without complications.¹⁹ Clevidipine, a new short-acting titratable dihydropyridine calcium channel blocker, and angiotensin-converting enzyme inhibitors have theoretical benefits in this setting, but to date there is no published experience using these drugs in the management of tetanus. Data are limited regarding the use of titratable vasodilators, such as nitroglycerin and sodium nitroprusside. Due to the duration of the hemodynamic derangement, the latter drug comes with a risk of thiocyanate toxicity. Finally, to achieve cardiovascular stability in four patients, atropine has been used in extremely high doses without complication, and this approach deserves further research.²⁵

Anesthetic management for surgical procedures

Surgical procedures in tetanus patients are occasionally necessary, such as debridement of the injury and tracheostomy. Little evidence exists to recommend specific anesthetic protocols. Similar to the recommendation to pretreat patients prior to nursing care,⁷ patients should be

deeply anesthetized and possibly paralyzed to prevent triggering hypertensive crises and spasms during the procedure. Most intravenous anesthetic agents and sedatives have been used in tetanus patients. Epidural mepivacaine³ and high continuous spinal bupivacaine⁷ have been used successfully to treat autonomic instability without complications related to the neuraxial technique, but norepinephrine infusions were required to maintain mean arterial pressure. Spinal anesthesia has been used for lower extremity debridement in a patient with mild tetanus who was not tracheally intubated.¹⁶ There is no literature examining the safety of volatile anesthetics. Malignant hyperthermia has not been associated with tetanus, although the anesthesiologist should be aware of some similarities between the clinical presentations of tetanus and malignant hyperthermia. As mentioned, hyperkalemic arrest from succinylcholine administration has been documented. If a patient requires a general anesthetic, the anesthesiologist's considerations should include: (1) the need for deep anesthesia and/or paralysis to prevent paroxysms and risk of aspiration; (2) use of depolarizing neuromuscular agents; (3) difficult respiratory management with potential for airway compromise if the patient is not intubated; (4) hypoxemia and hypoventilation; (5) toxin-mediated or catecholamine-induced cardiomyopathy⁷; and, regardless of the anesthetic technique chosen; (6) potentially life-threatening autonomic instability (Table 1). This instability

has the potential to make intra-operative events, such as hemorrhage, devastating. Once established in the course of the disease, all the considerations of a critically ill patient apply to tetanus patients. Electrolyte derangements from tetanus-induced renal dysfunction should be corrected preoperatively.⁷ Appropriate invasive monitoring should be secured, and titratable drug infusions for intra-operative management of autonomic storms should be prepared before proceeding with a surgical procedure. Ideally, patients being considered for debridement and tracheostomy should undergo anesthesia and surgery before severe autonomic dysfunction develops.

Conclusions

Even in the hands of those most experienced with tetanus, there seems to be little evidence-based consensus on treatment protocols. Recent improvements in treatment in the initial phases of tetanus present new challenges for physicians, as patients are increasingly surviving to the more advanced stages of the disease. Many crucial barriers still exist to overcoming this disease in developing countries, including a lack of reliable immunization programs, a shortage of trained medical personnel, and a scarcity of resources such as medications and ventilators. Physicians from developed countries will increasingly come into

Table 1 Pathophysiological effects of tetanus

<i>Airway</i>	<i>Motor</i>
Trismus	Muscular spasm, paroxysms, generalized rigidity, opisthotonus
Cervical rigidity	Rhabdomyolysis
Pharyngeal, laryngeal spasm	
Copious oral secretions	
Aspiration risk	<i>Gastrointestinal</i>
	Ileus
<i>Breathing</i>	Malnutrition
Diaphragmatic spasm or paralysis	Gastrointestinal hemorrhage*
Chest wall rigidity, abdominal rigidity	
Hypoventilation	<i>Renal</i>
Bronchial secretions	Acute tubular necrosis
Ventilation/perfusion mismatch	Myoglobinuria and renal failure
Pneumonia*	
Adult Respiratory Distress Syndrome*	<i>Metabolic/endocrine</i>
Pulmonary embolus*	Hypermetabolic state
	Pyrexia
<i>Circulation</i>	Diaphoresis
Autonomic storms	
Cardiomyopathy	<i>Hematologic/immunologic</i>
Sudden cardiac arrest	Sepsis*
Hyperkalemic response to depolarizing neuromuscular blocking drugs	

* Indicates a complication of a prolonged critical illness

contact with patients at risk for tetanus, both at home and abroad. This case series illustrates the value of an exchange of medical experience and expertise between very different medical systems, such as we experienced with our colleagues in Rwanda.

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Conflicts of interest None declared.

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