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Guidelines for the management of accidental tetanus in adult patients

Diretrizes para o manejo do tétano acidental em pacientes adultos

These guidelines are provided by the Associação de Medicina Intensiva Brasileira (AMIB).

ABSTRACT

Although tetanus can be prevented by appropriate immunization, accidental tetanus continues to occur frequently in underdeveloped and developing countries. Tetanus mortality rates remain high in these areas, and studies regarding the best therapy for tetanus are scarce. Because of the paucity of data on accidental tetanus and the clinical relevance of this condition, the Associação de Medicina Intensiva Brasileira (AMIB) organized a group of experts to develop these guidelines, which are based on the best available evidence for the management of tetanus in patients requiring admission to the intensive care unit. The guidelines discuss the management of tetanus patients in the intensive care unit, including the use of immunoglobulin therapy, antibiotic therapy, management of analgesics, sedation and neuromuscular blockade, management of dysautonomia and specific issues related to mechanical ventilation and physiotherapy in this population.

INTRODUCTION

Tetanus is caused by *Clostridium tetani* and may be prevented by immunization. Tetanus may be categorized as either accidental or neonatal; neonatal tetanus has a poorer prognosis and a higher rate of mortality.[1-6] Accidental tetanus continues to be frequent in underdeveloped and developing countries. The mortality rate of accidental tetanus varies among different studies and depends on multiple factors, including patient age; clinical severity; the type of infectious source wound; incubation and progression times; concomitant respiratory, hemodynamic, renal and infective complications; the site where the patient is treated; and the quality of the care provided.[1-6]

Clostridium tetani produces exotoxins, such as tetanolysin and tetanospasmin. Tetanolysin's function in human tetanus is not clear; however, it is believed to damage healthy tissues around the wound and to reduce oxidation-reduction potential, thereby promoting the growth of anaerobic organisms. Tetanospasmin is a neurotoxin and is commonly known as tetanus toxin. All recognized tetanus manifestations result from tetanospasmin's ability to inhibit neurotransmitter release from the presynaptic membrane for several weeks; symptoms result from involvement of central motor control, autonomic function and the neuromuscular junction. The clinical features of tetanus depend on the class and location of affected cells. During the induction of palsy, GABA-ergic and glycinergic cells are inhibited, and the motor system responds to afferent stimuli with intense, simultaneous and sustained contractions of agonist and antagonist muscles, which are known as tetanic spasms. The effects of tetanus on the

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autonomic nervous system usually begin by the second week as a typical autonomic dysfunction syndrome that is characterized by labile hypertension, tachycardia, cardiac arrhythmias, peripheral vasoconstriction, diaphoresis, pyrexia and eventually hypotension and bradycardia, suggesting that the sympathetic and parasympathetic systems are affected.[3]

The severity of accidental tetanus depends on the distribution of muscle spasms, with localized cases involving a few muscle groups and generalized cases involving the entire skeletal musculature.[7]

Because of the paucity of data on tetanus and the clinical relevance of accidental tetanus, the Associação de Medicina Intensiva Brasileira (AMIB) organized a group of experts who developed these guidelines, which are based on the best available evidence for the management of tetanus in patients requiring admission to the intensive care unit. The guidelines discuss the management of tetanus patients in the intensive care unit (ICU), including the use of immunoglobulin and antibiotic therapies, the management of analgesia, sedation and neuromuscular blockade, the management of dysautonomia and mechanical ventilation and physiotherapy issues in this population.

METHODS

The questions were prepared and revised by the group of experts. The primary aspects of the treatment of tetanus were considered, and the PICO concept was used, where P stands for the target population, I for the intervention, C for the control or comparative group and O for the clinical outcome.

The recommendation degrees are provided by the GRADE (Grades of Recommendation, Assessment, Development and Evaluation) system.[8] This system is based on assessment of the quality of the evidence followed by a risk/benefit assessment. Based on this analysis, the recommendations were categorized as STRONG (grade 1) or WEAK (grade 2), as shown in table 1. A strong recommendation either for or against a given intervention means that the desirable effects of this intervention clearly outweigh its untoward effects or vice versa. A weak recommendation either for or against a given intervention means that the benefits of this intervention are likely to outweigh its risks and burdens (or vice versa), but the group is not confident in the recommendation because of insufficient or poor quality evidence. In practical terms, a strong recommendation could be interpreted as "recommended to be done (or not recommended)." Conversely, a weak recommendation could be interpreted as "suggested (or not suggested)."

Articles retrieved through the literature search were critically analyzed and categorized according to their evidence level, as shown in Table 1. Therefore, recommendations were given a character and a number, reflecting both the level of evidence and the strength of the recommendation.

Table 1 - GRADE System

1. Strong recommendation
2. Weak recommendation.
A: Randomized and controlled trials.
B: Randomized and controlled trials with limitations leading to downgrading of the evidence level or well performed observational studies with an upgraded evidence level.
C: Well conducted observational studies.
D: Expert opinions or case series.

The questions and search strategies were discussed and distributed for the group members during the first meeting. Later, each response was forwarded for discussion via electronic media. Next, the board of experts gathered in person; the recommendations and rationales were discussed and approved by consensus. No voting methodology was used. The final document was approved by all participating experts before its publication.

Description of the evidence collection method

The primary literature search was conducted on MEDLINE, which was accessed via the PubMed service. Searches were based on questions that were structured according to the P.I.C.O. methodology. The search strategy used for answering each question is shown, along with the recommendation and rationale supporting the intervention. Additionally, a generic search using the keyword 'tetanus' was conducted using the Scientific Electronic Library On-line (SCIELO) and Cochrane Collaboration databases.

TETANUS MANAGEMENT RECOMMENDATIONS

1. Does admission to the intensive care unit impact tetanus patients' morbidity and mortality?

Search strategy

Tetanus AND (critical care OR intensive care OR ICU OR critically ill).

We recommend management in the intensive care unit (ICU) for patients with moderate and severe accidental tetanus for better monitoring, rapid

detection of complications and intensive care by a trained team, regardless of their age group (1B).

We suggest ICU admission for patients with mild tetanus, particularly if poor-prognosis risk factors are present (2C).

We suggest that in cases with limited ICU bed availability, patients who have mild tetanus without poor-prognosis risk factors can be managed outside the ICU in regular wards staffed by personnel experienced in the care of patients with tetanus, provided that such patients are admitted to the ICU if worsening of their clinical condition is detected (2D).

Rationale

Several studies emphasize the importance of admitting tetanus patients, especially those with more severe clinical presentations, to intensive care units. ICU admission is particularly beneficial for elderly patients, whose mortality rates are higher.[1,2,9-18] In the ICU, appropriate monitoring and quick detection of complications can be performed by a trained multidisciplinary team.[12-14,17,19,20]

We highlight five studies that showed reduced mortality after ICU admission in tetanus patients. In Japan, a decrease in mortality from 40-50% for patients treated between 1940 and 1970, to 20% for patients treated between 1971and 1980, and 10% for patients treated between 1981 and 1982 was shown.[15] In Spain, mortality decreased from 58.3% to 24.6% between 1968 and 1990;[10] in Venezuela, mortality dropped from 43.58% to 15%;[2] and in India, mortality decreased from 70% to 23% of severe tetanus cases.[14] A Brazilian study from Recife-PE showed a drop from a mortality of 35% in 1631 patients treated outside of the ICU between 1981-1996 to 12.6% in 638 patients treated after the ICU was established ($p < 0.001$).[18]

However, several authors have persistently high mortality rates in spite of ICU care.[4,21-23] This finding suggests that in addition to the ICU facility itself, trained staff and advanced technology appropriate to such severely ill patients' needs are important. This hypothesis is supported by a Brazilian study in which the mortality rate dropped from 36.5% before 1993 to 18% after 1993 ($p=0.002$) after the quality of care improved and a strict treatment protocol was adopted. This finding was observed despite differences in the second group that included longer ICU stays, increased use of benzodiazepines, neuromuscular blockade and mechanical ventilation, and a higher rate of infectious complications.[1]

Another study showed that patients admitted to the ICU had worse outcomes and higher mortality rates than patients managed in regular wards.[21] Patients were transferred to the ICU only when more severe disease or complications occurred, while mild cases were treated outside the ICU. These patients had lower risks of respiratory and hemodynamic complications, which are currently the main causes of death in tetanus patients.

The management of mild tetanus cases in regular wards may be an alternative in cases of limited ICU bed availability; patients may be admitted to the intensive care unit when poor prognostic signs are identified at admission. Risk factors include: short incubation time (< 10 days), short progression time (<48 hours), age above 60 years, severe comorbidities, or infective, respiratory, hemodynamic or renal complications at the time of admission.

However, most of the experts recommend admitting all patients to the ICU immediately following a diagnosis of accidental tetanus, regardless of the disease severity, due to the risk of rapid disease progression and complications.[12,19]

2. Is a clinical strategy of grading the severity of disease relevant to the management of tetanus patients?

Search strategy

Tetanus AND (severity OR grading OR classification OR severity score).

We suggest that each service should routinely use one of the several accidental tetanus disease severity classification currently available in the medical literature. Patients should be categorized upon admission due to the prognostic value of disease severity classification. The most severe forms require more aggressive therapy and are more frequently associated with complications and increased mortality (2D).

Rationale

Several authors have proposed severity grading methods based on clinical parameters (such as intensity of the muscle contractures, spasm frequency, and response to muscle relaxant drugs) and/or prognostic factors (such as incubation and progression times). Classification systems that are based only on clinical data, when used repeatedly over time, describe whether the symptoms are improving or worsening. The patients' changing from one clinical form to another can predict the patients' responses to therapeutic measures and the outcome of the illness.[6] Therefore, patients may be divided into grades (numerically) or clinical forms (mild to very severe), depending on the classification used.[5,6,24-26]

Independent of the categorization used, patients classified as having more severe disease have a worse prognosis and are more likely to develop respiratory, infectious and cardiovascular complications. Such patients therefore require a more aggressive approach.[5,6,24,25,27-33]

Mortality is also related to the severity classification. Although the mortality rate of mild tetanus is low, patients with severe and very severe disease are more likely to die and should be intensively monitored and treated. [23,26,34-39]

3. Does systemic immunoglobulin administration impact tetanus patients' morbidity and mortality?

Search strategy

Tetanus AND immunoglobulin.

We recommend passive immunization using human anti-tetanus immunoglobulin (HATIG) or equine immunoglobulin (anti-tetanus serum; ATS) and it should be given as soon as possible following diagnosis (1B).

We recommend that HATIG, when available, should be given preferentially to ATS, as the immediate and late adverse events profile of HATIG is safer than that of ATS (1C).

We suggest a single deep intramuscular dose, specifically, 500 to 5000 IU HATIG or 20,000 to 30,000 IU ATS (2C).

We recommend active immunization (vaccination) at the same time as passive immunization (1C).

Rationale

The goal of anti-toxin administration is to neutralize circulating tetanospasmin. Anti-toxin should be administered as soon as possible following a tetanus diagnosis.[40]

No studies are available comparing the use of the equine anti-tetanus serum (ATS) to human specific anti-tetanus immunoglobulin (HATIG). The disadvantages of ATS are related to hypersensitivity reactions. Reactions may be mild (itching/skin redness, urticaria), moderate (dry cough, hoarseness, bronchospasm, nausea/vomiting), severe or even fatal (anaphylactic shock). Symptoms of a late reaction ("serum sickness") include fever, urticaria, arthralgia, adenopathy and, more rarely, neurological and renal involvement. These symptoms may develop 5 to 21 days after ATS administration and should be treated with analgesics, antihistamines and corticosteroids.[41]Another advantage of HATIG advantage is related to its half-life (21-30 days), which provides a more prolonged effect.

The ideal dose of ATS is not established in the medical literature. No differences in morbidity or mortality were seen between higher and lower doses.[42-44] Recent data suggest doses between 500 and 1,000 IU/kg.[7,45] There is also no consensus regarding the dose of specific human immunoglobulin for the treatment of tetanus. The doses used range from 500 IU to 10,000 IU.[1,44-46] There are no randomized clinical trials comparing different doses and tetanus morbidity and mortality. In an observational analysis by Blake et al.,[46] no difference was found between doses of 500 and 10,000 IU.

4. Does perilesional immunoglobulin impact outcomes in tetanus patients?

Search strategy

Tetanus AND (antitoxin OR immunoglobulin) AND [perilesional OR wound]. Manuscripts involving animal experimental models, animal tetanus studies, case reports, studies approaching tetanus prophylaxis and studies that were written in languages other than English or Portuguese were excluded.

We suggest perilesional anti-tetanus immunoglobulin should not be used (2D).

Rationale

Perilesional anti-tetanus immunoglobulin is used by some practitioners and aims to block tetanospasmin at the inoculation focus, thereby preventing its dissemination during treatment of the wound. However, no comparative studies on this procedure are available. With the current widespread use of HATIG, some authors have challenged this therapy.[7,40,45]

5. Does intrathecal immunoglobulin (compared to intramuscular administration) impact tetanus patients' morbidity and mortality?

Search strategy

Tetanus AND *immunoglobulin*. Studies on prophylaxis, development of immunoglobulin or vaccines were excluded.

We suggest intrathecal anti-tetanus immunoglobulin should not be used (2C).

Rationale

Trials using intrathecal antitoxin have been conducted since 1970.[47] This procedure aims to neutralize GABA receptor-bound toxins, given that systemically administered antitoxin has no effect in these sites.

Randomized clinical trials have been conducted both in children and adults. The first adult studies, which used equine anti-tetanus serum, failed to show a benefit from this procedure. Additionally, such complications as meningeal irritation were seen, requiring the concomitant use of systemic or intrathecal corticosteroids.[48]

After specific human anti-tetanus immunoglobulin became available, new intrathecal trials were conducted, starting in the 1980s. These studies showed a benefit in terms of some secondary outcomes, such as shortened duration of muscle spasms and length of ICU stay. However, intrathecal antitoxin had no impact on mortality.[49-52] Most patients included in these studies had mild or moderate tetanus; additionally, treatment methods and observation times were quite heterogeneous. The antitoxin doses in these studies were also highly variable, ranging from 200 IU to 1,000 IU. When patients with severe tetanus were analyzed separately, no benefit was shown, even for secondary outcomes.[49,50] Therefore, this procedure is not recommended, especially in cases of severe tetanus.

6. Does early debridement of the wound impact tetanus patients' morbidity and mortality?

Search strategy

Tetanus AND [debridement OR focus control]. The analysis of the articles showed no comparative clinical trial of early or late wound debridement.

Inoculation focus debridement is recommended (1D).

We suggest performing this procedure 1 to 6 hours after immunoglobulin administration, given that the best timing for this procedure has not been established (2D).

Rationale

Debridement of the *C. tetani* inoculation focus has been performed since the first tetanus cases were described. The rationale for this procedure is based on the presumption that toxin production is maintained for as long as *C. tetani* is present and that toxin production could be stopped by removing the bacteria.[40,53,54] No studies are available comparing early versus late debridement of the inoculation focus. The recommendation for performing debridement 1 to 6 hours after systemic HATIG or ATS is administered is based on the rationale that this interval would allow appropriate toxin neutralization at the wound, thereby preventing toxin dissemination during manipulation of the wound.[55]

7. Does the antibiotic schedule (either metronidazole, crystalline penicillin or benzylpenicillin) impact tetanus patients' morbidity and mortality?

Search strategy

Tetanus AND [antibiotic OR antimicrobial OR metronidazole OR penicillin OR doxycycline].

We recommend using antibiotics active against *Clostridium tetani* with the goal of eradicating it from the inoculation focus (1C).

We suggest either metronidazole or penicillin can be used; neither of these drugs has proved to be superior to the other one (2B).

We suggest using other antibiotics only if the use of metronidazole and/or penicillin is contraindicated (2D).

Rationale

Although no clinical trials support a clinical benefit of antibiotics for *Clostridium tetani* eradication, antibiotics are always indicated for the treatment of tetanus patients.[7] This goal of this treatment is eradication of the toxin-producing bacteria from the inoculation focus.

Benzylpenicillin was the first antibiotic used for treating tetanus. However, penicillins produce a non-competitive and voltage-dependent inhibition of GABA-A receptors, suppressing the postsynaptic inhibitory response,[56] and may theoretically increase the excitatory effects of tetanospasmin.

Metronidazole is a safe alternative for the treatment of tetanus. This drug is affordable, highly bioavailable, has good gastric and rectal absorption and has bactericidal action against anaerobic bacteria. Additionally, gastric pH interferes little with metronidazole (compared to erythromycin and doxycycline) and undergoes no enzymatic inactivation (as do the β-lactam antibiotics).[57]

No evidence is available on the superiority of one drug over the other,[54,58,59] although some data show more benefits from the use of metronidazole.[58,59]

Little evidence is available regarding the clinical use of other antibiotics for the eradication of *C. tetani*. Such alternatives as erythromycin, tetracycline, doxycycline, ceftazidime, vancomycin, clindamycin and chloramphenicol are only justifiable if penicillin or metronidazole are not available.[7]

8. Compared to placebo, does vitamin C have an impact on the morbidity and mortality of severe tetanus patients?

Search strategy
Tetanus AND [ascorbic acid OR vitamin C].

We suggest vitamin C is not indicated for the reduction of morbidity and mortality due to severe tetanus (2D).

Rationale
Of the assessed articles, only one described a clinical trial of vitamin C in tetanus patients.[60] This was a single-center, non-randomized, open study in which patients were allocated to the treatment group (with vitamin C) or the non-treatment group by being admitted to different wards. Vitamin C was given at the dose of 1 g IV/day for the entire treatment course. The study included 117 patients, divided according to age: 1 to 12 years (n=62) and 13 to 30 years (n=55). In both groups, adding vitamin C to the conventional treatment was associated with significantly reduced mortality: 100% (95% CI -100% to -94%) for the 1-12 year-old group and 45% (95% CI -69% to -5%) for the 13-30 year-old group.

However, this study has been severely criticized in a Cochrane review. Reasons for the criticism included the lack of a clear definition for the diagnosis of tetanus, non-randomized allocation to treatment (allowing selection bias) and possible heterogeneity in the age groups.[61]

It was recently suggested that the use of vitamin C should be assessed again, given the high mortality of tetanus, especially in developing countries.[62]

9. Does immediate tracheostomy impact tetanus patients' morbidity and mortality compared to late tracheostomy?

Search strategy
Tetanus AND [tracheostomy OR airway management]

We suggest that tracheostomy should be performed as soon as possible within the first 24 hours after orotracheal intubation in patients with moderate and severe tetanus requiring airway protection or mechanical ventilation. This procedure should be conducted under optimal conditions (2D).

Rationale
No articles were found assessing the impact on morbidity and mortality of performing a tracheostomy in tetanus patients; only case reports were identified, reporting the need for this procedure following intubation, due to prolonged respiratory failure.

In the past, major causes of morbidity and mortality in tetanus included respiratory failure due to respiratory muscle impairment and laryngeal spasm, complications associated with the use of neuromuscular blockers, and mechanical ventilation problems, such as respirator disconnection or difficulty with ventilation due to chest muscle rigidity.[12]

Orotracheal intubation may be performed initially. However, the presence of the endotracheal tube may trigger or exacerbate laryngeal and generalized spasms. To avoid this complication, which can cause unnecessary need for muscle relaxants, and to facilitate ventilatory support, tracheostomy should be performed early.[63] In underdeveloped countries with limited access to mechanical ventilation and intensive care facilities, tracheostomy may serve as airway protection and can aid in attempts to maintain spontaneous breathing for as long as possible in patients with uncontrolled life-threatening spasms.[2,25,64]

10. Does the ventilation mode impact the length of mechanical ventilation, length of ICU stay, morbidity or mortality?

Search strategy
Tetanus AND [mechanical ventilation OR ventilation mode OR Ventilation strategy] and tetanus AND [OR airway management].

We suggest using assisted volume or pressure controlled ventilation, as there is no evidence indicating the superiority of any of these modes of ventilation. (2D)

Rationale
No studies were identified regarding the effects of different assisted ventilation modes in tetanus patients. Frequently, mode of ventilation is limited by the available equipment in the ICU. Areas with more tetanus cases are likely to be those with the most rudimentary devices.[7,17,45]

Several studies have shown the importance of mechanical ventilation for tetanus patients.[23,65] A prospective study of 226 patients, divided into two groups in different decades, used two mechanical ventilation modes: pressure- and/or volume-controlled. Mortality due to respiratory causes was lower in the second group, due to fewer mechanical ventilation-related events, including pneumothorax, pneumomediastinum, ventilator disconnection and tube occlusion. However, no difference was found in the ventilation modes between the assessed periods, given that the second group used more modern devices, lower tidal volumes and positive end-expiratory pressure (PEEP).[1]

Volume-controlled ventilation sets a stable tidal volume

and pre-adjusted minute volume but requires adjustment of the flow wave, inspiratory flow and inspiration time. When airway pressure is increased, due to reduced compliance, increased resistance or active expiration, the risk of ventilator-related pulmonary injury may increase. With pressure-controlled ventilation, the maximal pressure delivered by the ventilator will be limited. The inspiratory pressure should be titrated for measuring the tidal volume, but the inspiratory flow and wave-shape are determined by the device, which attempts to maintain the inspiratory pressure profile.

Many studies comparing both methods in other critical care patient populations are well-designed but offer little information on how to use each ventilatory variable. At the present time, there is no apparent advantage for any of the ventilation modes. In tetanus patients, muscle spasms may change the chest wall compliance or increase airway resistance due to increased secretions, therefore increasing the risk of barotrauma in the volume-controlled ventilation mode. However, with the pressure-controlled mode, the same mechanisms may lead to reduced tidal volume, reduced minute volume and desaturation. For this condition, the patient must receive adequate muscle relaxation to maintain appropriate ventilation. It should be emphasized that, for any ventilation mode, maintaining protective ventilation, with 6-8 ml/kg/body weight tidal volume and PEEP, reduces ventilator-induced pulmonary injury.[66,67]

During the late phases of tetanus, when the patient has completely recovered from his or her muscle spasms, weaning from the ventilator may be attempted with ventilation modes that allow spontaneous pressure-support ventilation.[17]

11. Does diazepam (compared with midazolam or baclofen) for muscle relaxation impact the morbidity and mortality of patients with severe tetanus?

Search strategy

Tetanus AND [midazolam OR diazepam OR benzodiazepine OR baclofen OR sedation], limited to the past 20 years. Animal studies, case reports and general case series not specifically related to this subject were excluded, as were studies in pediatrics and neonatology.

We suggest using diazepam for muscle relaxation; this drug may be given either as a bolus or a continuous infusion, once appropriately diluted for continued infusion (2D).

We suggest baclofen or midazolam as alternative therapies (2D).

Rationale

Muscle relaxation is the main objective of tetanus therapy. Muscle relaxation is needed to allow ventilation, reduce pain and prevent hypertonia and spasms. No controlled trials (whether randomized or not) have assessed the effectiveness and safety of benzodiazepines (diazepam or midazolam) or baclofen for the treatment of tetanus in adult patients. A 2004 meta-analysis extensively reviewed the literature in adults and children.[68] The authors identified only two randomized or quasi-randomized trials, both of which were conducted in children, with a total of 134 patients.[69,70] This meta-analysis showed that patients treated with diazepam only have improved survival compared to those treated with a combination of phenobarbital and chlorpromazine. However, several methodological limitations limit any conclusions, even in the pediatric population. Several case reports and case series have been published using other treatment schedules, e.g., intrathecal baclofen,[71-76] dexamedetomidine[77] or midazolam with or without propofol,[78,79] or propofol alone.[80,81] Experience with diazepam is more extensive, supporting it as the first choice of a muscle relaxant until appropriate studies can be conducted. However, given the probable effectiveness and safety of midazolam and baclofen, these drugs may be considered to be appropriate therapeutic options.

Diazepam is a potent GABA-ergic agonist. This drug has a fast onset of action when given as a bolus, which is useful for spasm control. The dose required to provide relaxation may be high, ranging from 1 to 10 mg/kg/day according to the desired degree of relaxation. This drug can be used as a bolus (10-30 mg/hour) or a continued infusion with extra 10-mg boluses as required. The use of bolus is difficult, due to the high doses that are used. Additionally, continuous infusion provides a more stable effect and allows more appropriate dose titration. However, continued infusion requires special care to prevent precipitation and assure a correlation between the given dose and the clinical effects. A glass bottle and standardized dilutions should be used (4 mL of 0.9% saline or 5% glucose for each mg of diazepam, with infusions up to every 8 hours). An undesirable effect of continuous infusion is the potential for excessive infusion of volume. In both cases, part of the dose may be given enterally when possible. The prolonged administration of diazepam in tetanus may be associated with extended recovery times, due to the production of its metabolite, desmethyldiazepam. Desmethyldiazepam has a prolonged half-life and may build up in excessive doses. Midazolam

may represent an alternative to diazepam, and continuous infusion of midazolam does not have the same adverse effect profile of diazepam. However, midazolam may cause delirium, is more expensive, and has more frequent hemodynamic effects.

Baclofen is another therapeutic alternative to diazepam. This drug is a GABA-ergic receptor agonist, which inhibits the presynaptic elimination of acetylcholine, leading to muscle relaxation. Because baclofen does not cross the blood-brain barrier, intrathecal administration of baclofen may optimize its effect in tetanus. This drug may be given as a continued infusion or intermittently; the maximal daily dose is 2 mg. The infusion may be started at 20 μg/hour and progressively increased every 4 to 8 hours until the desired effects are obtained. The infusion rate may be increased by 8-10 μg/hour. The maximum treatment time reported in the literature is 3 weeks.[72] Classical side effects including drowsiness, vertigo, nausea and confusion are not relevant in tetanus patients. Eventually, hypotension and delirium may occur.[73] However, there is a risk of infection associated with a long-term epidural catheter, even when it is tunneled.[72] Baclofen is not available as an intrathecal formulation in Brazil. Therefore, its use is limited to oral administration during the convalescence phase of tetanus; doses can range up to 60 mg/day.

12. Is the use of neuromuscular blockers associated with improved clinical outcomes in severe tetanus patients under mechanical ventilation?

Search strategy

Tetanus AND [neuromuscular blockade OR pancuronium OR vecuronium OR atracurium OR rocuronium OR cisatracurium]

We suggest using neuromuscular blockers, preceded by appropriate sedation and analgesia, to provide muscle relaxation and control spasms in patients with severe tetanus who are undergoing mechanical ventilation and are refractory to other muscle relaxants (2D).

We suggest that choice of drug should follow the same criteria as for other critically ill patients (2D).

Rationale

The drugs of choice to provide sedation, spasm control and muscle relaxation in tetanus patients are benzodiazepines with opioids, which are used to provide appropriate analgesia. Even in high doses, this combination may be insufficient to control muscle spasms, and the use of neuromuscular blockade may be required, especially in mechanically ventilated patients with severe tetanus.

No randomized and controlled studies are available to assess the possible positive or negative effects of this association in tetanus patients. The vast majority of the relevant articles are case reports or small patient series. Five retrospective studies include most of the assessed patients.[1,13,17,82,83]

In the assessed articles, pancuronium was the most commonly used drug followed by vecuronium, atracurium and rocuronium. This finding may be explained by the timing of the introduction of these drugs into clinical practice. Until the early 1980s, only pancuronium was available; the other drugs were introduced during the 1980s.[84] Therefore, recommendations for the use of neuromuscular blockers in tetanus patients are not different from commonly used guidelines for critically ill patients.[84]

Several adverse effects associated with the use of curare drugs should be considered. These effects are usually caused by prolonged immobility and may lead to muscle atrophy, eye injuries, nerve injuries due to compression and deep vein thrombosis.[85] There is evidence that prolonged muscle blockade may result in prolonged palsy and weakness in severely ill patients. These effects have been associated with eventual overdose, which is a preventable inconvenience with appropriate clinical monitoring.[85,86] The duration of neuromuscular blocker administration should be as short as possible. The use of protocols based on monitoring of the desired blockade can reduce the mechanical ventilation time, the length of ICU stay and costs.[87,88]

13. Is the use of any specific drug for analgesia and sedation of tetanus patients associated with improved outcomes?

Search strategy

Tetanus AND analgesia AND sedation AND outcome, resulting in one single article. The search was extended using the following keywords: *tetanus AND outcome AND (sedation OR analgesia OR clonidine OR dexmedetomidine OR propofol OR opioids OR morphine OR fentanyl OR remifentanyl OR phenobarbital OR anesthesia)*, *tetanus AND sedation* and *tetanus AND analgesia*.

We suggest analgesia and sedation of tetanus patients should be performed using opioids with central alpha agonists and/or propofol, although no evidence for the superiority of any of the several reported strategies is available (2D).

Rationale

For severe tetanus, the use of several simultaneous analgesic/sedative drugs, such as benzodiazepines, opioids, central alpha agonists, propofol and epidural anesthesia has been described in the literature in case reports or case series. No comparison regarding the effectiveness of these strategies is available.

Benzodiazepines have been traditionally used for control of muscle contractures and spasms, due to their sedative effects. High daily doses of diazepam have been suggested as unfavorable outcome markers.[89,90] However, it should be noted that higher diazepam doses are used in more severely ill patients at sites that have difficulty accessing ventilatory care, which could impact the outcomes.[30]

For analgesia and sedation in tetanus patients, opioids have always been used in combination with other drugs. Reports on the intravenous use of fentanyl,[91], alfentanyl, remifentanyl[92] and epidural sulfentalyl (in association with bupivacaine)[93] show that this group of drugs is an option, especially in patients with autonomic hyperactivity.

Propofol, due to its sedative and muscle relaxant action,[81] has been proposed for the treatment of tetanus, both in loading doses[94] and as a continuous infusion.[80] The experience with propofol is restricted to isolated case reports and case series. Propofol is usually given in combination with benzodiazepines, opioids and muscle relaxants,[95] which prevents a comparison of therapeutic schedules and outcomes.

Dexmedetomidine is an imidazole derivative with high affinity for alpha-2-adrenoceptors. This drug's analgesic properties and ability to reduce plasma catecholamine levels were assessed in a series of tetanus cases.[77] Following a 1 mcg/kg loading dose, a continuous infusion was administered (0.2 to 0.7 mcg/kg/hour) for seven days. For complete spasm control, a combination of diazepam and vecuronium was necessary. The authors concluded that the drug is safe and can and control pain and spasms when given with low dose diazepam and curare. Clonidine, another central alpha agonist, was used in up to 3 mcg/kg/day doses along with midazolam, sulfentanyl, propofol and thiopental with the aim of promoting deep analgesia and sedation in tetanus patients with severe dysautonomia.[96,97]

No studies comparing the different analgesia/sedation schedules and their impacts on clinical outcomes were identified.

14. Does daily creatine phosphokinase (CPK) monitoring impact the prevention of acute kidney injury (AKI) associated with rhabdomyolysis or the adjustment of muscle relaxation in tetanus patients?

Search strategy:

Tetanus AND [rhabdomyolysis OR creatine-phosphokinase OR acute renal failure].

We suggest daily measurement of CPK levels in tetanus patients with the aim of monitoring response to muscle relaxant therapy (2D).

We suggest not measuring CPK levels aiming to detect rhabdomyolysis or to prevent acute kidney injury (2C).

Rationale

The first reports of increased CPK levels in tetanus patients are from the 1960s.[98] Increased muscle enzymes were initially interpreted as a possible diagnostic strategy in patients with tetanus.[99] After tetanus toxin administration, CPK release occurs 3 to 4 days before muscle stiffness develops.[100] Elevations in muscle enzymes have been reported even after tetanus toxoid administration,[101] and CPK levels may be quite high (above 22,000).[102]

Acute kidney injury is frequent in tetanus patients and is associated with increased mortality. Although sparse reports are available on the development of renal failure in tetanus patients, in patients with moderate CPK increases (around 6,000 U/L),[103] rhabdomyolysis as cause of acute kidney injury is not common. The increase in CPK levels is usually moderate and is generally not associated with kidney injury. No correlation between CPK levels and kidney injury has been shown.[104,105] Other potential causes, such as hypovolemia, sepsis, nephrotoxic drugs and (especially) dysautonomia, are apparently more relevant.[105,106]

Therefore, daily monitoring of CPK levels is not justified for the early detection of rhabdomyolysis or for the prevention of renal injury prevention. However, daily changes in of CPK levels may help to detect inappropriate muscle relaxation, allowing for adjustments in the dose of muscle relaxants. Although no data have shown this practice to be useful in reducing morbidity and mortality, it is frequently used in intensive care units caring for tetanus patients.

15. Does the use of any specific drug have an impact on the clinical outcomes in severe tetanus patients with dysautonomia?

Search strategy

Tetanus AND (dysautonomia OR hemodynamic instability OR autonomic dysfunction). Animal studies, case reports and general case series not specifically related to

this subject were excluded, as were studies in pediatrics and neonatology.

We suggest using opiates (morphine or fentanyl), in a continuous infusion, as the first option for the management of dysautonomia (2D).

We suggest using adjuvant therapy for control of labile blood pressure; however, the best therapeutic option cannot be established (2D).

Rationale

Autonomic dysfunction in septic patients is characterized by loss of autonomic inhibition, thereby resulting in labile blood pressure, tachycardia, diaphoresis, and eventually, refractory hypotension and cardiorespiratory arrest.[107,108] The wide spectrum of disease prevents the use of one single agent to control this syndrome.

The changes are apparently mediated by increased serum catecholamine levels, which may reach up to 10 times their baseline levels.[107,109,110] However, this theory is controversial because it is difficult to establish that increased catecholamine levels are a consequence of inappropriate sedation and muscle spasm control.[111] Additionally, a correlation between serum catecholamine levels and the clinical features of dysautonomia in tetanus patients has not been clearly shown.[107] The identification of tetanospasmin as a zinc-dependent peptidase enzyme leads to a new hypothesis to explain hypertension in tetanus patients.[112] It has been suggested that among other actions, tetanospasmin has an effect that is similar to angiotensin-converting enzyme and that hypertension is more closely related to excess angiotensin II levels than to catecholaminergic effects. This hypothesis suggests that angiotensin-converting enzyme inhibitors could be used in tetanus patients.[113] The lability of blood pressure levels means that drugs with a shorter half-life are preferred; this property would allow rapid reversal of or compensation for their effects.[30,107]

Most of the clinical experience in medically managing dysautonomia has been with opiates. Morphine has been shown to be effective in tetanus-related autonomic disorders, although its mode of action is unclear. A possible mechanism is compensation for the release of endogenous opiates. Tetanospasmin inhibits the action of encephalins, which may play a role in modulating the autonomic system. The loading dose is 5 mg followed by continuous infusion of 0.05 to 0.1 mcg/kg/min or with 5-mg doses every 3 hours. Morphine is apparently more effective when combined with alpha-2-agonists as adjuvant therapy for dysautonomia and control of blood pressure lability.[114]

Clonidine is an alpha-2-agonist with sedative properties; it has been shown to effectively control dysautonomia in some case reports[107,114-116] and in a small prospective study.[117] Alpha-2 receptor effects on the central nervous system, such as sedation and vasodilation, make this drug an important alternative treatment. Findings in the literature suggest that clonidine is safe and effective for the treatment of dysautonomia. Data on the use of dexmedetomidine, another alpha-2-agonist, are restricted to anecdotal reports.[77,107]

The use of beta-blockers is controversial and has been associated with sudden death, probably due to beta-blockade with alpha-adrenergic activity release. The use of beta-blockers is not recommended.[118] However, there are reports suggesting that continuous infusion of labetalol[110,119] and esmolol[120,121] may help to control dysautonomia.

Other medications, such as propofol, ACE inhibitors, verapamil and atropine, have been proposed as alternatives for the management of dysautonomia. However, the reports on the use of these drugs are anecdotal.[78,80,81,97,113,122] Several reports describe that epidural administration of such agents as bupivacaine with the creation of a continued epidural blockade may contribute to the management of autonomic dysfunction.[98,123,124] However, the role of this therapy is uncertain.

Rapid- and short-acting drugs, such as noradrenaline and nitroprusside, are alternatives treatments for controlling wide pressure fluctuations. However, the use of these drugs requires close surveillance with continuous blood pressure monitoring.

16. Does continuous administration of magnesium ($MgSO_4$) in severe tetanus patients impact the outcome compared to the placebo?

Search strategy

Tetanus AND magnesium sulfate. Animal studies, case reports and general case series not specifically related to this subject were excluded, as were studies in pediatrics and neonatology.

We suggest using $MgSO_4$ in severe tetanus patients in association with benzodiazepines and neuromuscular blockers to control muscle spasms (2B).

Rationale

$MgSO_4$ has been used in tetanus patients for more than

100 years[125] and has several potentially useful features for the management of severe tetanus. These features include muscle relaxation, vasodilation, reduced heart rate and reduced systemic catecholamine levels.[109,114,126,127] Magnesium may therefore be an effective adjunct therapy for muscle spasm and autonomic dysfunction control.

Several case reports and series have been published that suggest benefit from the use of $MgSO_4$.[114,126,128] However, only one randomized, double-blind clinical trial comparing $MgSO_4$ and placebo has appropriately addressed this issue. In an observational prospective study, Attygale et al. showed that $MgSO_4$ reduced the use of sedatives and neuromuscular blockers and decreased ventilatory support requirements when administered for 7 days.[127]

These findings were partially confirmed in a randomized, placebo-controlled clinical trial conducted in 2006.[129] In this study, 256 patients were randomized to receive continued intravenous $MgSO_4$ infusion or the placebo for 7 days. A loading dose of 40 mg/kg for 30 minutes was used followed by a 2 g/hour infusion. The randomization was appropriately performed via a computer-generated randomization list, and the blinding was appropriate. No significant difference was observed in the primary endpoint (requirement of ventilation support during the first 7 days) with an OR of 0.71 (95% CI 0.36-1.40). However, a significant difference was found in the secondary endpoints, i.e., reduced needs of benzodiazepines, neuromuscular blockers and verapamil, which were considered to be the treatment of choice for dysautonomia in this study location. This result suggests a role for $MgSO_44$ as a potential adjuvant for control of spasms, and it may also be useful agent for the management of autonomic dysfunction in patients with severe sepsis.

17. Does respiratory physiotherapy in severe tetanus patients impact outcomes?

Search strategy
Tetanus AND [physiotherapy OR passive mobilization].

We suggest motor and respiratory physiotherapy in mechanically ventilated tetanus patients (2D).

We suggest an increase in analgesia/sedation and/or neuromuscular blockade before physiotherapy (2D).

Rationale
Physiotherapy is part of the multidisciplinary care of several types of intensive care unit patients, e.g., patients undergoing prolonged mechanical ventilation.[130] No articles have been published on the role of physiotherapy in tetanus patients. However, there is no evidence that physiotherapy in these patients, if appropriately performed, causes adverse effects. Therefore, physiotherapy should be performed according to each site's protocol. Passive motor physiotherapy may prevent joint deformities and muscle shortening. Also, orthopedic splints may be used to maintain the physiological position of the feet, preventing deformity. Because any stimulus may trigger spasms in tetanus patients, analgesia/sedation and/or neuromuscular blockage should be increased before physiotherapy and returned to previous levels after the therapy session.

CLOSING REMARKS AND FUTURE PERSPECTIVES

Although it is preventable through vaccination, accidental tetanus remains a common problem in underdeveloped and developing countries and has extremely high mortality rates. Most evidence regarding the optimal management of tetanus comes from anecdotal reports and case series. This report is the first initiative to gather experts for a critical review of the literature regarding adult tetanus patients in the intensive care unit setting in order to provide specific guidelines for the management of tetanus.

Despite advances in the knowledge of the pathophysiology of tetanus and the development of specific therapies for the disease, certain aspects of the ICU management of tetanus patients need to be more objectively evaluated. We described a number of these issues and attempted to suggest interventions that can affect the outcomes of patients with tetanus based on a critical assessment of the scarce literature and the experts' experience regarding this subject. However, definite answers regarding the usefulness of specific strategies in the intensive care unit management of accidental tetanus in adults will only come from collaborative clinical trials and clinical investigation networks on both the national and international levels.

RESUMO

O tétano acidental, a despeito de ser uma doença prevenível por imunização, ainda é frequente nos países subdesenvolvidos e em desenvolvimento. Sua letalidade ainda é elevada e os estudos sobre a melhor forma de tratamento são escassos. Tendo em vis-

ta esta escassez e a importância clínica dessa doença, um grupo de especialistas reunidos pela Associação de Medicina Intensiva Brasileira (AMIB), desenvolveu recomendações baseadas na melhor evidencia disponível para o manejo do tétano no paciente necessitando cuidados intensivos. As recomendações incluem aspectos relativos à admissão do paciente tetânico na unidade de terapia intensiva, tratamento com imunoglobulinas, tratamento antibiótico, manejo da analgossedação e bloqueio neuromuscular, manejo da disautonomia e especificidades na ventilação mecânica e fisioterapia nesta população especial.

REFERÊNCIAS

1. Brauner JS, Vieira SR, Bleck TP. Changes in severe accidental tetanus mortality in the ICU during two decades in Brazil. Intensive Care Med. 2002;28(7):930-5.
2. Trujillo MH, Castillo A, España J, Manzo A, Zerpa R. Impact of intensive care management on the prognosis of tetanus. Analysis of 641 cases. Chest. 1987;92(1):63-5.
3. Bleck TP, Brauner JS. Tetanus. In: Scheld WM, Witley RJ, Marra CM, editors. Infections of the central nervous system. 3rd ed. New York: Lippincott Williams & Wilkins; 2004. p. 625-48.
4. Orellana-San Martín C, Su H, Bustamante-Durán D, Velásquez-Pagoaga L. [Tetanus in intensive care units]. Rev Neurol. 2003;36(4):327-30. Spanish.
5. Fukutake T, Miyamoto R. [Clinical features of tetanus: a review with case reports]. Brain Nerve. 2011;63(10):1101-10. Japanese.
6. Miranda-Filho DB, Ximenes RA, Barone AA, Vaz VL, Vieira AG, Albuquerque VM. Clinical classification of tetanus patients. Braz J Med Biol Res. 2006;39(10):1329-37.
7. Farrar JJ, Yen JM, Cook T, Fairweather N, Binh N, Parry J, Parry CM. Tetanus. J Neurol Neurosurg Psychiatry. 2000;69(3):292-301.
8. Atkins D, Best D, Briss PA, Eccles M, Falck-Ytter Y, Flottorp S, Guyatt GH, Harbour RT, Haugh MC, Henry D, Hill S, Jaeschke R, Leng G, Liberati A, Magrini N, Mason J, Middleton P, Mrukowicz J, O'Connell D, Oxman AD, Phillips B, Schünemann HJ, Edejer TT, Varonen H, Vist GE, Williams JW Jr, Zaza S; GRADE Working Group. Grading quality of evidence and strength of recommendations. BMJ. 2004;328(7454):1490.
9. Jolliet P, Magnenat JL, Kobel T, Chevrolet JC. Aggressive intensive care treatment of very elderly patients with tetanus is justified. Chest. 1990;97(3):702-5.
10. Ramírez Miñana R, Sicilia Lafont T, Aguilera JL, César JM, Domínguez B, Soto J. [Tetanus in adults: mortality. Study in 130 cases]. Enferm Infecc Microbiol Clin. 1990;8(6):338-43. Spanish.
11. Anuradha S. Tetanus in adults --a continuing problem: an analysis of 217 patients over 3 years from Delhi, India, with special emphasis on predictors of mortality. Med J Malaysia. 2006;61(1):7-14.
12. Edmondson RS, Flowers MW. Intensive care in tetanus: management, complications, and mortality in 100 cases. Br Med J. 1979;1(6175):1401-4.
13. Camacho JA, Jiménez JM, Díaz A, Montijano A, Quesada JL, Montiel D. [Severe-grade tetanus in a multipurpose ICU: review of 13 cases]. Enferm Infecc Microbiol Clin. 1997;15(5):243-5. Spanish.
14. Udwadia FE, Lall A, Udwadia ZF, Sekhar M, Vora A. Tetanus and its complications: intensive care and management experience in 150 Indian patients. Epidemiol Infect. 1987;99(3):675-84.
15. Ebisawa I, Homma R. Tetanus in Japan: trends of mortality, case fatality and causes of death. Jpn J Exp Med. 1986;56(4):155-61.
16. Joshi S, Agarwal B, Malla G, Karmacharya B. Complete elimination of tetanus is still elusive in developing countries: a review of adult tetanus cases from referral hospital in Eastern Nepal. Kathmandu Univ Med J (KUMJ). 2007;5(3):378-81.
17. Dutta TK, Das AK, Sethuraman KR, Swaminathan RP. Neuroparalysis and ventilatory support in severe tetanus. J Indian Med Assoc. 2006;104(2):63-6.
18. Gouveia PAC, Silva CEF, Miranda Filho DB, Bernardino SN, Escarião AG, Ximenes RAA. Tendência temporal do tétano acidental no período de 1981 a 2004 em Pernambuco com avaliação do impacto da assistência em unidade de terapia intensiva sobre a letalidade. Rev Soc Bras Med Trop. 2009;42(1):54-7.
19. Bassin SL. Tetanus. Curr Treat Options Neurol. 2004;6(1):25-34.
20. Boyles CS, Mills MH, Trupiano P. Tetanus: critical implications for nursing. Crit Care Nurse. 1998;18(3):44-9.
21. Ojini FI, Danesi MA. Mortality of tetanus at the Lagos University Teaching Hospital, Nigeria. Trop Doct. 2005;35(3):178-81.
22. Duning T, Schäbitz WR. [Treatment strategies for tetanus]. Nervenarzt. 2007;78(2):145-6, 149-52, 155. German.
23. Chalya PL, Mabula JB, Dass RM, Mbelenge N, Mshana SE, Gilyoma JM. Ten-year experiences with Tetanus at a Tertiary hospital in Northwestern Tanzania: A retrospective review of 102 cases. World J Emerg Surg. 2011;6:20.
24. Armitage P, Clifford R. Prognosis in tetanus: Use of data from therapeutic trials. J Infect Dis. 1978;138(1):1-8.
25. Thwaites CL, Yen LM, Glover C, Tuan PQ, Nga NT, Parry J, et al. Predicting the clinical outcome of tetanus: the tetanus severity score. Trop Med Int Health. 2006;11(3):279-87.
26. Durán-Nah J, Ceh-Gómez E, Díaz-Cervera I, Mis-

Fernández R. [Epidemiologic features of tetanus in adults form Yucatan, Mexico]. Rev Invest Clin. 2001;53(6):536-42. Spanish.

27. Sathirapanya P, Sathirapanya C, Limapichat K, Setthawacharawanich S, Phabphal K. Tetanus: a retrospective study of clinical presentations and outcomes in a medical teaching hospital. J Med Assoc Thai. 2009;92(3):315-9.
28. Henriques Filho GT, Lacerda HR, Albuquerque A, Ximenes RA. Sympathetic overactivity and arrhythmias in tetanus: electrocardiographic analysis. Rev Inst Med Trop Sao Paulo. 2007;49(1):17-22.
29. Ogunrin OA, Unuigbe EI. Tetanus: an analysis of the prognosticating factors of cases seen in a tertiary hospital in a developing African country between 1990 and 2000. Trop Doct. 2004;34(4):240-1.
30. Attygalle D, Rodrigo N. New trends in the management of tetanus. Expert Rev Anti Infect Ther. 2004;2(1):73-84.
31. Ogunrin OA, Unuigbe EI. Tetanus: an analysis of the prognosticating factors of cases admitted into the medical wards of a tertiary hospital in a developing African country between 1990 and 2000. Niger Postgrad Med J. 2004;11(2):97-102.
32. Cavalcante NJ, Sandeville ML, Medeiros EA. Incidence of and risk factors for nosocomial pneumonia in patients with tetanus. Clin Infect Dis. 2001;33(11):1842-6.
33. Luisto M. Outcome and neurological sequelae of patients after tetanus. Acta Neurol Scand. 1989;80(6):504-11.
34. Patel JC, Mehta BC. Tetanus: study of 8,697 cases. Indian J Med Sci. 1999;53(9):393-401.
35. Fawibe AE. The pattern and outcome of adult tetanus at a sub-urban tertiary hospital in Nigeria. J Coll Physicians Surg Pak. 2010;20(1):68-70.
36. Hesse IF, Mensah A, Asante DK, Lartey M, Neequaye A. Adult tetanus in Accra, why the high mortality? An audit of clinical management of tetanus. West Afr J Med. 2005;24(2):157-61.
37. Arogundade FA, Bello IS, Kuteyi EA, Akinsola A. Patterns of presentation and mortality in tetanus: a 10-year retrospective review. Niger Postgrad Med J. 2004;11(3):198-202.
38. Oladiran I, Meier DE, Ojelade AA, OlaOlorun DA, Adeniran A, Tarpley JL. Tetanus: continuing problem in the developing world. World J Surg. 2002;26(10):1282-5.
39. Carrillo Alcaraz A, Palazón Sánchez EL, Silla López A, Pardo Talavera JC, Castillo Soria F, Gómez Rubí JA. [Tetanus in the Murcia region: the clinico-epidemiological characteristics of 150 cases]. Rev Clin Esp. 1993;192(8):369-75. Spanish.
40. Ataro P, Mushatt D, Ahsan S. Tetanus: a review. South Med J. 2011;104(8):613-7.
41. Ross DE, Kraut JJ. Tetanus: prophylaxis and treatment of the disease. Calif Med. 1959;90(5):322-7.
42. Vakil BJ, Tulpule TH, Armitage P, Laurence DR. A comparison of the value of 200,000 I.U. of tetanus antitoxin (horse) with 10,000 I.U. in the treatment of tetanus. Clin Pharmacol Ther. 1968;9(4):465-71.
43. Lucas AO, Willis AJ, Mohamed SD, Montgomery RD, Steiner H, Armitage P, Laurence DR. A comparison of the value of 500,000 I.U. tetanus antitoxin (horse) with 200,000 I.U. in the treatment of tetanus. Clin Pharmacol Ther. 1965;6(5):592-7.
44. Saltoglu N, Tasova Y, Midikli D, Burgut R, Dündar IH. Prognositic factors affecting deaths from adult tetanus. Clin Microbiol Infect. 2004;10(3):229-33.
45. Bhatia R, Prabhakar S, Grover VK. Tetanus. Neurol India. 2002;50(4):398-407. Review.
46. Blake PA, Feldman RA, Buchanan TM, Brooks GF, Bennett JV. Serologic therapy of tetanus in the United States, 1965-1971. JAMA. 1976;235(1):42-4.
47. Levin ASS, Baroni AA, Shiroma M. Soroterapia intratecal no tétano. Revisão. Rev Inst Med Trop S Paulo. 1987;29(5):255-67.
48. Thomas PP, Crowell EB Jr, Mathew M. Intrathecal anti-tetanus serum (ATS) and parenteral betamethasone in the treatment of tetanus. Trans R Soc Trop Med Hyg. 1982;76(5):620-3.
49. Gupta PS, Kapoor R. Intrathecal tetanus immunoglobulin (human). Indian J Pediatr. 1982;49(396):15-7.
50. Agarwal M, Thomas K, Peter JV, Jeyaseelan L, Cherian AM. A randomized double-blind sham-controlled study of intrathecal human anti-tetanus immunoglobulin in the management of tetanus. Natl Med J India. 1998;11(5):209-12
51. Miranda-Filho Dde B, Ximenes RA, Barone AA, Vaz VL, Vieira AG, Albuquerque VM. Randomised controlled trial of tetanus treatment with antitetanus immunoglobulin by the intrathecal or intramuscular route. BMJ. 2004;328(7440):615.
52. Kabura L, Ilibagiza D, Menten J, Van den Ende J. Intrathecal vs. intramuscular administration of human antitetanus immunoglobulin or equine tetanus antitoxin in the treatment of tetanus: a meta-analysis. Trop Med Int Health. 2006;11(7):1075-81. Review.
53. Smith JW, MacIver AG. Growth and toxin production of Tetanus bacilli in vivo. J Med Microbiol. 1974;7(4):497-504.
54. Ahmadsyah I, Salim A. Treatment of tetanus: an open study to compare the efficacy of procaine penicillin and metronidazole. Br Med J (Clin Res Ed). 1985;291(6496):648-50.
55. Brook I. Current concepts in the management of Clostridium tetani infection. Expert Rev Anti Infect Ther. 2008;6(3):327-36.
56. Sugimoto M, Fukami S, Kayakiri H, Yamazaki S, Matsuoka N, Uchida I, Mashimo T. The beta-lactam antibiotics, penicillin-G and cefoselis have different mechanisms and

sites of action at GABA(A) receptors. Br J Pharmacol. 2002;135(2):427-32.
57. Löfmark S, Edlund C, Nord CE. Metronidazole is still the drug of choice for treatment of anaerobic infections. Clin Infect Dis. 2010;50 Suppl 1:S16-23.
58. Ganesh Kumar AV, Kothari VM, Krishnan A, Karnad DR. Benzathine penicillin, metronidazole and benzyl penicillin in the treatment of tetanus: a randomized, controlled trial. Ann Trop Med Parasitol. 2004;98(1):59-63.
59. Campbell JI, Lam TM, Huynh TL, To SD, Tran TT, Nguyen VM, et al. Microbiologic characterization and antimicrobial susceptibility of Clostridium tetani isolated from wounds of patients with clinically diagnosed tetanus. Am J Trop Med Hyg. 2009;80(5):827-31.
60. Jahan K, Ahmad K, Ali MA. Effect of ascorbic acid in the treatment of tetanus. Bangladesh Med Res Counc Bull. 1984;10(1):24-8.
61. Hemilä H, Koivula TT. Vitamin C for preventing and treating tetanus. Cochrane Database Syst Rev. 2008;(2):CD006665.
62. Hemila H. Vitamin C and the treatment of tetanus. Ann Afr Med. 2010;9(2):108-9.
63. Hsu SS, Groleau G. Tetanus in the emergency department: a current review. J Emerg Med. 2001;20(4):357-65.
64. Gibson K, Bonaventure Uwineza J, Kiviri W, Parlow J. Tetanus in developing countries: a case series and review. Can J Anaesth. 2009;56(4):307-15. Review.
65. Kerr JH, Corbett JL, Spalding JM. Sympathetic overactivity in severe tetanus. Proc R Soc Med. 1969;62(7):659-62.
66. Petrucci N, Iacovelli W. Ventilation with lower tidal volumes versus traditional tidal volumes in adults for acute lung injury and acute respiratory distress syndrome. Cochrane Database Syst Rev. 2004;(2):CD003844. Review. Update in: Cochrane Database Syst Rev. 2007;(3):CD003844.
67. Petrucci N, Iacovelli W. Lung protective ventilation strategy for the acute respiratory distress syndrome. Cochrane Database Syst Rev. 2007;(3):CD003844. Update of Cochrane Database Syst Rev. 2004;(2):CD003844.
68. Okoromah CN, Lesi FE. Diazepam for treating tetanus. Cochrane Database Syst Rev. 2004;(1):CD003954.
69. Hendrickse RG, Sherman PM. Tetanus in childhood: report of a therapeutic trial of diazepam. Br Med J. 1966;2(5518):860-2.
70. Tjoen LW, Darmawan S, Ismael S, Sudigbia I, Suradi R, Munthe BG. The effect of diazepam on tetanus. Paediatr Indones. 1970;10(6):248-58.
71. Cabrerizo García JL, Homs Gimeno CA, Pacheco Arancibia G, Zalba Etayo B, Sánchez Marteles M. [Treatment of tetanus with intrathecal baclofen]. An Med Interna. 2008;25(7):372-3. Spanish.
72. Santos ML, Mota-Miranda A, Alves-Pereira A, Gomes A, Correia J, Marçal N. Intrathecal baclofen for the treatment of tetanus. Clin Infect Dis. 2004;38(3):321-8.
73. Chawla JM, Sagar R. Baclofen-induced psychosis. Ann Pharmacother. 2006;40(11):2071-3.
74. Boots RJ, Lipman J, O'Callaghan J, Scott P, Fraser J. The treatment of tetanus with intrathecal baclofen. Anaesth Intensive Care. 2000;28(4):438-42.
75. Dressnandt J, Konstanzer A, Weinzierl FX, Pfab R, Klingelhöfer J. Intrathecal baclofen in tetanus: four cases and a review of reported cases. Intensive Care Med. 1997;23(8):896-902.
76. Saissy JM, Demazière J, Vitris M, Seck M, Marcoux L, Gaye M, Ndiaye M. Treatment of severe tetanus by intrathecal injections of baclofen without artificial ventilation. Intensive Care Med. 1992;18(4):241-4.
77. Girgin NK, Iscimen R, Gurbet A, Kahveci F, Kutlay O. Dexmedetomidine sedation for the treatment of tetanus in the intensive care unit. Br J Anaesth. 2007;99(4):599-600.
78. Kamikawa M, Watanabe M, Hirano T, Yonemitsu K, Kinoshita Y, Uchino M. [Antispasm therapy using combination of midazolam and propofol for severe tetanus]. Rinsho Shinkeigaku. 2005;45(7):506-9. Japanese.
79. Gyasi HK, Fahr J, Kurian E, Mathew M. Midazolam for prolonged intravenous sedation in patients with tetanus. Middle East J Anesthesiol. 1993;12(2):135-41.
80. Borgeat A, Popovic V, Schwander D. Efficiency of a continuous infusion of propofol in a patient with tetanus. Crit Care Med. 1991;19(2):295-7.
81. Borgeat A, Dessibourg C, Rochani M, Suter PM. Sedation by propofol in tetanus--is it a muscular relaxant? Intensive Care Med. 1991;17(7):427-9.
82. Caban J, Postawa B. [Patients with severe tetanus treated in the department of infectious diseases in 1986-1988]. Przegl Lek. 1990;47(9):633-6. Polish.
83. Harding-Goldson HE, Hanna WJ. Tetanus: a recurring intensive care problem. J Trop Med Hyg. 1995;98(3):179-84.
84. Murray MJ, Cowen J, DeBlock H, Erstad B, Gray AW, Jr, Tescher AN, McGee WT, Prielipp RC, Susla G, Jacobi J, Nasraway SA Jr, Lumb PD; Task Force of the American College of Critical Care Medicine (ACCM) of the Society of **Critical** Care Medicine (SCCM), American Society of Health-System Pharmacists, American College of Chest Physicians. Clinical practice guidelines for sustained neuromuscular blockade in the adult critically ill patient. Crit Care Med. 2002;30(1):142-56.
85. Watling SM, Dasta JF. Prolonged paralysis in intensive care unit patients after the use of neuromuscular blocking agents: a review of the literature. Crit Care Med. 1994;22(5):884-93.
86. Nates J, Cooper D, Day B, Tuxen DV. Acute weakness syndromes in critically ill patients--a reappraisal. Anaesth Intensive Care. 1997;25(5):502-13.
87. Zarowitz BJ, Rudis MI, Lai K, Petitta A, Lulek M. Retrospective pharmacoeconomic evaluation of dosing vecuronium by peripheral nerve stimulation versus standard clinical assessment in critically ill patients.

Pharmacotherapy. 1997;17(2):327-32.
88. Rudis MI, Guslits BJ, Peterson EL, Hathaway SJ, Angus E, Beis S, Zarowitz BJ. Economic impact of prolonged motor weakness complicating neuromuscular blockade in the intensive care unit. Crit Care Med. 1996;24(10):1749-56.
89. Arogundade FA, Bello IS, Kuteyi EA, Akinsola A. Patterns of presentation and mortality in tetanus: a 10-year retrospective review. Niger Postgrad Med J. 2004;11(3):198-202
90. Chukwubike OA, God'spower AE. A 10-year review of outcome of management of tetanus in adults at a Nigerian tertiary hospital. Ann Afr Med. 2009;8(3):168-72.
91. Moughabghab AV, Prevost G, Socolovsky C. Fentanyl therapy controls autonomic hyperactivity in tetanus. Br J Clin Pract. 1996;50(8):477-8.
92. Beecroft CL, Enright SM, O'beirne HA. Remifentanil in the management of severe tetanus. Br J Anaesth. 2005;94(1):46-8.
93. Bhagwanjee S, Bösenberg AT, Muckart DJ. Management of sympathetic overactivity in tetanus with epidural bupivacaine and sufentanil: experience with 11 patients. Crit Care Med. 1999;27(9):1721-5.
94. Petitjeans F, Turc J, Coulet O, Puidupin M, Eve O, Benois A. The use of boluses of propofol for the management of severe tetanus in a child. Trop Doct. 2009;39(1):52-3.
95. Orko R, Rosenberg PH, Himberg JJ. Intravenous infusion of midazolam, propofol and vecuronium in a patient with severe tetanus. Acta Anaesthesiol Scand. 1988;32(7):590-2.
96. Duning T, Kraus J, Nabavi DG, Schaebitz WR. Management of autonomic dysfunction in severe tetanus: the importance of deep analgosedation. Intensive Care Med. 2007;33(2):380-1.
97. Peduto VA, Pisanu GM, Piga M. [Midazolam, propofol, and clonidine for sedation and control of autonomic dysfunction in severe generalized tetanus]. Minerva Anestesiol. 1993;59(4):171-8. Italian.
98. Mullan D, Dubowitz V. Serum enzymes in diagnosis of tetanus. Lancet. 1964;2(7358):505-7.
99. Alvárez Sánchez B, García Sanz M, Merino de Cos P, Caturla Such J, Fuster Lozano M, Serrano T, Soria Muñoz F, Aguado Pérez M. [Diagnosis of acute generalized tetanus using total CPK values. Prognostic-developmental correlates]. Rev Clin Esp. 1982;165(1):43-6. Spanish.
100. Brody IA, Hatcher MA. Origin of increased serum creatine phosphokinase in tetanus. An isoenzyme analysis. Arch Neurol. 1967;16(1):89-93.
101. Fischer D, Reimann J, Schröder R. [Macrophagic myofasciitis: inflammatory, vaccination-associated muscular disease]. Dtsch Med Wochenschr. 2003;128(44):2305-8. German.
102. Hursitoglu M, Cikrikcioglu MA, Gundogan E, Ozkan O, Cordan I, Yigit Y, et al. Rhabdomyolysis secondary to tetanus toxoid administration in a patient following minor laceration. J Clin Pharmacol. 2011;51(1):110-1.
103. Weiss MF, Badalamenti J, Fish E. Tetanus as a cause of rhabdomyolysis and acute renal failure. Clin Nephrol. 2010;73(1):64-7.
104. Martinelli R, Matos CM, Rocha H. Tetanus as a cause of acute renal failure: possible role of rhabdomyolysis. Rev Soc Bras Med Trop. 1993;26(1):1-4.
105. Daher EF, Abdulkader RC, Motti E, Marcondes M, Sabbaga E, Burdmann EA. Prospective study of tetanus-induced acute renal dysfunction: role of adrenergic overactivity. Am J Trop Med Hyg. 1997;57(5):610-4.
106. Lima EQ, Silva RG, Fernandes IM, Abbud-Filho M, Burdmann EA. Tetanus-induced acute kidney injury in a renal transplant recipient. Am J Trop Med Hyg. 2007;77(2):400-2.
107. Freshwater-Turner D, Udy A, Lipman J, Deans R, Stuart J, Boots R, et al. Autonomic dysfunction in tetanus - what lessons can be learnt with specific reference to alpha-2 agonists? Anaesthesia. 2007;62(10):1066-70.
108. Cook TM, Protheroe RT, Handel JM. Tetanus: a review of the literature. Br J Anaesth. 2001;87(3):477-87.
109. Lipman J, James MF, Erskine J, Plit ML, Eidelman J, Esser JD. Autonomic dysfunction in severe tetanus: magnesium sulfate as an adjunct to deep sedation. Crit Care Med. 1987;15(10):987-8.
110. Domenighetti GM, Savary G, Stricker H. Hyperadrenergic syndrome in severe tetanus: extreme rise in catecholamines responsive to labetalol. Br Med J (Clin Res Ed). 1984;288(6429):1483-4.
111. Brauner JS, Clausell N. Neurohumoral, immunoinflammatory and cardiovascular profile of patients with severe tetanus: a prospective study. J Negat Results Biomed. 2006;5:2.
112. Montecucco C, Schiavo G. Tetanus and botulism neurotoxins: a new group of zinc proteases. Trends Biochem Sci. 1993;18(9):324-7. Review.
113. Dayanithi G, Stecher B, Höhne-Zell B, Yamasaki S, Binz T, Weller U, et al. Exploring the functional domain and the target of the tetanus toxin light chain in neurohypophysial terminals. Neuroscience. 1994;58(2):423-31.
114. Sutton DN, Tremlett MR, Woodcock TE, Nielsen MS. Management of autonomic dysfunction in severe tetanus: the use of magnesium sulphate and clonidine. Intensive Care Med. 1990;16(2):75-80.
115. Kamibayashi T, Maze M. Clinical uses of alpha2 -adrenergic agonists. Anesthesiology. 2000;93(5):1345-9.
116. Kumar A, Anand R, Rahal A, Od S. Use of intratechal and intravenous clonidine in a case of severe tetanus with acute renal failure. Indian J Anaesth. 2009;53(2):204-8.
117. Gregorakos L, Kerezoudi E, Dimopoulos G, Thomaides T. Management of blood pressure instability in severe tetanus: the use of clonidine. Intensive Care Med. 1997;23(8):893-5.
118. Buchanan N, Smit L, Cane RD, De Andrade M.

Sympathetic overactivity in tetanus: fatality associated with propranolol. Br Med J. 1978;2(6132):254-5.
119. Wesley AG, Hariparsad D, Pather M, Rocke DA. Labetalol in tetanus. The treatment of sympathetic nervous system overactivity. Anaesthesia. 1983;38(3):243-9.
120. King WW, Cave DR. Use of esmolol to control autonomic instability of tetanus. Am J Med. 1991;91(4):425-8.
121. Beards SC, Lipman J, Bothma PA, Joynt GM. Esmolol in a case of severe tetanus. Adequate haemodynamic control achieved despite markedly elevated catecholamine levels. S Afr J Surg. 1994;32(1):33-5.
122. Dolar D. The use of continuous atropine infusion in the management of severe tetanus. Intensive Care Med. 1992;18(1):26-31.
123. Shibuya M, Sugimoto H, Sugimoto T, Shimazu T, Uenishi M, Yoshioka T. The use of continuous spinal anesthesia in severe tetanus with autonomic disturbance. J Trauma. 1989;29(10):1423-9.
124. Mora Quintero ML, Ansuátegui M, López Mederos D, Gonzáles Miranda F. Epidural anesthesia for sympathetic overactivity in severe tetanus. Crit Care Med. 1987;15(8):801.
125. Blake JA. II. The treatment of tetanus by magnesium sulphate. Ann Surg. 1906;44(3):367-73.
126. James MF, Manson ED. The use of magnesium sulphate infusions in the management of very severe tetanus. Intensive Care Med. 1985;11(1):5-12.
127. Attygalle D, Rodrigo N. Magnesium as first line therapy in the management of tetanus: a prospective study of 40 patients. Anaesthesia. 2002;57(8):811-7.
128. Ho HS, Lim SH, Loo S. The use of magnesium sulphate in the intensive care management of an Asian patient with tetanus. Ann Acad Med Singapore. 1999;28(4):586-9.
129. Thwaites CL, Yen LM, Loan HT, Thuy TT, Thwaites GE, Stepniewska K, et al. Magnesium sulphate for treatment of severe tetanus: a randomised controlled trial. Lancet. 2006;368(9545):1436-43.
130. Jerre G, Silva TJ, Beraldo MA, Gastaldi A, Kondo C, Leme F, et al. Fisioterapia no paciente sob ventilação mecânica. J Bras Pneumol. 2007;33(Supl 2):S142-50.