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Lethality and osteomuscular and cardiovascular complications in tetanus

Letalidade e complicações osteomusculares e cardiovasculares no tétano

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ABSTRACT

Objective: Despite the decline in the incidence of tetanus, this disease is still neglected in the developing world and remains a major cause of morbidity and mortality. With improvements in intensive care, it is important to better understand the complications of this serious condition. We aim to evaluate 1) the lethality and osteomuscular and cardiovascular complications of patients with tetanus who are admitted to the intensive care unit (ICU) and 2) the risk factors associated with a poor prognosis.

Methods: This was a retrospective study that analyzed the medical records of all of the patients diagnosed with tetanus who were admitted to an infectious diseases ICU between January 2000 and December 2001. A standardized form that included demographic, clinical and laboratory data was completed. The clinical variables that were related to lethality and osteomuscular and cardiovascular complications were described.

Results: A total of 22 tetanus patients were admitted (81.8% male, mean age of 47.8 years). The tetanus infection was associated with professional activities in 54.5% of cases. The majority of patients (20 patients) presented with the generalized form of disease. Eighty-one percent of the patients had never received a tetanus vaccine or were unaware of their vaccine status.

Following the injury, none had received appropriated passive prophylaxis, only two patients had received surgical debridement of wound and six patients received antibiotic therapy. Eleven patients (52.4%) experienced some cardiovascular complication. A pressure ulcer was the most frequent cardiovascular complication (38.1%), followed by arrhythmias (28.6%). Two of the patients developed bone fractures secondary to tetanus spasms, corresponding to 9.6% of sample. The tetanus lethality rate was 9.1%. Higher APACHE II severity scores and very severe status based on the Veronesi tetanus classification were significantly associated with the risk of death ($p=0.04$ and 0.03 , respectively). The Veronesi classification was also associated with the risk of cardiovascular complications ($p=0.013$) and the length of the ICU stay ($p=0.009$).

Conclusion: The present study demonstrates the failure of primary medical care in vaccination and post-traumatic tetanus prophylaxis. Despite improvements in intensive care support, cardiovascular complications are still frequent in these patients. Individuals exhibiting high APACHE II scores and severe clinical forms of tetanus should be monitored closely due to a risk of death and cardiovascular complications.

Keywords: Tetanus/complications; Lethality

INTRODUCTION

Tetanus is a non-contagious infectious disease caused by tetanospasmin, a potent *Clostridium tetani* exotoxin. The disease is characterized by generalized or localized hypertony of the striated muscles.⁽¹⁻³⁾

The infection generally begins following inoculation of *C. tetani* spores via an injury or wound. Anaerobic conditions permit bacterial proliferation and toxin production. The tetanospasmin enters the perilesional muscles and soft tissues and subsequently reaches the synaptic cleft of neuromuscular junctions, motor neuron axons and the cell body (in the anterior horn of the spinal cord). Once in the cell body, the toxin undergoes transsynaptic transport to local inhibitory neuron axons. Finally, the toxin blocks the release of the neurotransmitters glycine and gamma-amino butyric acid from these inhibitory neurons. The clinical consequence of infection is chronic muscular contraction, or hypertony.⁽⁴⁾ Sensorial stimuli (particularly tactile and painful) may trigger simultaneous paroxysmal and sustained contractions of different muscular groups, including both agonists and antagonists. These involuntary contractions are termed tetanic spasms.⁽⁵⁾

According to Veronesi, the severity of the tetanus infection can be classified based on the incubation period (from lesion to trismus); the onset period (from trismus to the first generalized spasm); the progression of hypertony; the use of mechanical ventilation; the response to muscle relaxants (diazepam and/or curare); the development of dysautonomia; and the existence of cephalic presentation. Based on this classification method, tetanus can be classified as mild, severe or very severe.⁽³⁾

The most common tetanus complications are generally consequences of intensive care and include ventilator-associated pneumonia, catheter infection, sepsis, thromboembolism, stress ulcer development and deformities. Other complications include those that are secondary to the spasms and include rhabdomyolysis, renal failure, fracture of the vertebrae and tendon avulsions.⁽⁶⁻⁸⁾ When the disease is successfully treated, the symptoms completely regress.^(9,10)

The primary goal of tetanus treatment is patient survival. However, another objective is to achieve a reasonable quality of life.⁽¹¹⁾ Unfortunately, sequelae, such as a persistent vegetative state due to hypoxic brain damage and permanent disability, have been reported.⁽⁶⁾

Tetanus is present worldwide and can represent a serious public health problem, especially in developing countries with poorer social, economic and educational conditions.⁽¹²⁾ Given that prevention is inexpensive and effective, its

immunization coverage is considered a sensitive index of health service performance.^(13,14)

The number of tetanus cases in Brazil continuously declined between 1982 and 2004, from 2,810 to 497 cases per year.⁽¹⁴⁾ The reported incidence of tetanus dropped in São Paulo State, Brazil between the years of 1989 and 1999, likely because of the more widespread use of tetanus immunizations. In 1999, the Brazilian National Influenza, Pneumococcus, Tetanus and Diphtheria Vaccination Campaign for the Elderly was launched,⁽¹⁵⁾ decreasing the tetanus incidence rate in São Paulo State to lower than 0.1 per 100,000 person-years.⁽¹⁶⁾

This decline in tetanus incidence was not associated with a concurrent decrease in lethality in Brazil. The case-fatality rate is between 20 and 40 percent in São Paulo State. This rate is still high when compared to developed countries.⁽¹⁷⁾ Tetanus lethality is related to patient age, the clinical form and severity of disease, critical care support, the requirement for mechanical ventilation, the use of sedatives and neuromuscular blockers and dysautonomia control.⁽¹⁸⁾

Regardless of the specific treatment, the lethality of tetanus can be reduced by preventing respiratory, cardiovascular, osteomuscular and metabolic complications. The leading causes of death from tetanus are cardiovascular and respiratory complications, particularly ventilator-associated pneumonia.^(18,19) Better understanding these complications may improve the therapeutic approaches to prevent death, sequelae and/or functional limitations following infection.

This study aimed at evaluating the lethality, osteomuscular and cardiovascular complications of patients with tetanus who were admitted to an intensive care unit (ICU), and the risk factors associated with a poor prognosis.

METHODS

This study was conducted in a six-bed infectious disease ICU at the Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, a 2,200-bed teaching public hospital in São Paulo, Brazil. The majority of the patients were of a low socio-economic status.

All of the patients who were admitted to the ICU with tetanus between January 2000 and December 2001 were retrospectively included. There were no exclusion criteria. The Investigational Review Board of the Hospital das Clínicas approved the study (964/02), waiving the need for informed consent because of the retrospective nature of the study. Moreover, the need for informed consent was obviated given that confidentiality was guaranteed.

A standardized questionnaire was created (EPED EPI-Info program, version 6.03), and the data were collected from ICU admission until discharge. The demographic data were collected, as were the following tetanus characteristics: clinical presentation, portal of entry, the presence of a secondary infection, the incubation and onset periods, and the severity of the tetanus infection according to the Veronesi⁽³⁾ adapted classification scheme (Table 1). The tetanus vaccination status, the medical care of the injury, and tetanus infection-related first aid were also recorded. We also recorded the Acute Physiological Chronic Health Evaluation II (APACHE II) severity score, the ICU tetanus treatment, whether invasive mechanical ventilation was required, osteomuscular and cardiovascular complications, the occurrence of renal failure or nosocomial infections (pneumonia, urinary tract infection, bacteremia) and hospital survival.

We considered osteomuscular complications as fractures (except for those present at admission), equine foot and gait abnormalities. We defined cardiovascular complications as the presence of dysautonomia, septic shock, cardiogenic shock, acute pulmonary edema, coronary insufficiency, arrhythmias, deep venous thrombosis, pulmonary embolism, stroke and pressure ulcers. The diagnosis of other systemic complications (e.g., renal, pulmonary or infection-related) was made by the attending physician.

The ICU tetanus treatment protocol consisted of an intramuscular administration of 4,000-5,000 I.U. human tetanus immunoglobulin, 1,000 I.U. of the same via a perilesional route prior to surgical debridement, antibiotic therapy with penicillin or metronidazole, myorelaxation with diazepam, and sedation with phenobarbitone, as necessary.

All of the patients underwent routine 24-hour continuous 3-lead electrocardiography and blood pressure monitoring to identify possible arrhythmia episodes and/or dysautonomia. Additional 12-lead ECG recordings were performed if arrhythmia or coronary insufficiency were suspected. Continuous invasive blood pressure monitoring was performed as necessary to confirm the presence of arterial blood pressure oscillations. Dysautonomia was defined as the presence of marked

cardiovascular instability with abrupt fluctuations between states of severe arterial hypertension with tachycardia and severe hypotension with bradycardia.

Statistical analysis

We performed a descriptive analysis of the patients' demographic, epidemiological and clinical characteristics, severity scores, complications, and outcomes. We performed univariate analyses to evaluate which factors were associated with osteomuscular and cardiovascular complications and survival. The categorical variables were analyzed using a chi-squared or Fisher Exact Test. The continuous variables were expressed as the median (minimum-maximum) and compared using Student's t-test for normally distributed variables or the Mann-Whitney test for nonparametric variables. A significance level of $p < 0.05$ was used. The EPI-Info program, version 6.03, was used for the statistical analysis.

RESULTS

A total of 22 tetanus patients were admitted to the ICU, including 18 males (81.8%) (Table 2). The patients came from the countryside (9 patients), the coast (7 patients) and the capital of the São Paulo State (6 patients). The contraction of the disease was associated with professional activities in 54.5% of cases.

The medical records for one patient were unavailable; it was therefore not possible to obtain clinical data related to cardiovascular complications for this patient. The absolute majority of the patients (17 patients) developed generalized descending tetanus, three presented with generalized ascending tetanus and one with a localized pattern. Lower limb injuries accounted for the portal of entry in 85.7% of the cases. One of the patients developed tetanus due to necrosis of the distal ileum. A secondary wound infection was clinically present in 8 patients (38.1%).

The incubation period was determined for 18 patients, with a median time of 8 (1-15) days. The onset period was shorter than 48 hours in two patients, between 48 and 72 hours in five patients, and longer than 72 hours

Table 1 – Veronesi-adapted tetanus severity classification

	IP	OP	SF	MH	MV	RMR	DA	CP
Mild	>8 days	> 48 hours	0 to +	+	No	Favorable	No	No
Severe	<8 days	<48 hours	++	+++	Yes	Regular	No	Yes/No
Very severe	<8 days	<48 hours	++++	++++	Yes	Insufficient	Yes	Yes

IP - incubation period; OP - onset period; SF - spasm frequency; MH - muscular hypertonia; MV - mechanical ventilation; RMR - response to muscle relaxants; DA - dysautonomia; CP - cephalic presentation.

Adapted from Veronesi et al.⁽³⁾

Table 2 – Clinical comparison with respect to survival status in patients with tetanus

Characteristic	Survivors (N=20)	Non-survivors (N=2)	Global (N=22)	p value
Gender (male)	18 (90)	0(0)	18 (81.8)	0.03*
Age (years)	45.6 ± 16.8	70.0 ± 8.5	47.8 ± 17.5	0.06 [#]
Portal of entry				
Upper limb	2	0	2	0.83 [‡]
Lower limb	16	2	18	
Abdominal	1	0	1	
Not available	1	0	1	
Incubation period (days)	8 (1-15)	6 (6-6)	8 (1-15)	0.20 [§]
Mean onset period (hours)				
< 48	2	0	2	0.52 [‡]
48-72	5	0	5	
> 72	7	2	9	
Open	2	0	2	
Unknown	4	0	4	
Clinical presentation				
Descendent generalized	15	2	17	0.77 [‡]
Ascendant generalized	3	0	3	
Localized	1	0	1	
Unknown	1	0	1	
APACHE II				
< 13	18	0	18	0.04 [‡]
> 13	1	1	2	
Undetermined	1	1	2	
Veronesi classification				
Mild	7	0	7	0.03 [‡]
Severe	9	0	9	
Very severe	3	2	5	
Unknown	1	0	1	
Length of ICU stay (days)	23 (4-53)	48 (12-84)	23 (4-84)	0.40 [#]

APACHE - Acute Physiological Chronic Health Evaluation; ICU – intensive care unit. The results are expressed in number (percentage), mean ± standard deviation or median (minimum-maximum). *Fisher Exact Test; ‡ Chi-square; # Student's t-test; § Mann-Whitney test.

in nine patients. In one patient with generalized rigidity, generalized spasms were completely avoided using a pharmacological approach.

The APACHE II severity scores were available for twenty patients. All but two of the patients presented scores below 13 in the first 24 hours of admission. According to Veronesi tetanus severity scale, 23.8% of patients presented a very severe infection, 42.9% presented a severe infection and 33.3% presented a mild disease.

Seventeen patients had never received a tetanus vaccine or were unaware of their vaccine status (81%). Two of the patients had received the basic diphtheria/tetanus/pertussis scheme without any subsequent booster dose. Two of the patients received an incomplete basic

immunization scheme. Twelve of the patients had sought medical care soon after the injury, but none received appropriate passive prophylaxis. Only five of the patients had received an anti-tetanus vaccine. Only two of the patients had received surgical debridement of the wound, and six patients had received antibiotic therapy.

Nineteen patients (90.5%) sought general emergency services following the development of the first signs of tetanus. Prior to transfer to our center, only four of the patients had received surgical debridement, six had received an anti-tetanus immunoglobulin/serum, three were vaccinated against tetanus, nine received antibiotics, and the myorelaxant diazepam was administered in twelve patients.

Following admission to our ICU, all of the patients received penicillin or metronidazole with or without another antibiotic. In sixteen patients, surgical debridement was performed on the wound within the first 24 hours of admission. All of the patients were treated with continuous intravenous diazepam. Additional sedation with phenobarbitone was provided for thirteen patients (61.9%). Four of the patients failed to respond to the myorelaxant action of diazepam in high doses (10 mg/kg/day) and required neuromuscular blocking agents (19%). The mean peak of serum creatine phosphokinase levels was $5,670 \pm 10,485$ U/L, with a median peak of 1,456 U/L (445–5,528).

During the ICU stay, eleven patients (52.4%) developed a cardiovascular complication: one developed dysautonomy, five developed septic shock, two developed cardiogenic shock, two developed acute pulmonary edema, one developed coronary insufficiency, six developed arrhythmias, two developed pulmonary embolism, one developed deep venous thrombosis, and eight developed pressure ulcers (38.1%).

Although the tetanus patients frequently developed episodes of sinus tachycardia, particularly during muscular spasms, some developed more serious arrhythmic episodes, including severe sinus bradycardia/bradyasystole (5 patients) or persistent supraventricular extrasystoles (1 patient).

Fourteen of the patients (66.7%) required mechanical ventilation. Thirteen patients developed respiratory complications (61.9%), twelve developed atelectasis, eight developed nosocomial pneumonia, and two developed pneumothorax.

Five of the patients were complicated with acute renal failure (23.8%), three of whom required dialysis (15.8%). Thirteen of the patients developed infectious complications (59.1%). Two of the patients developed osteomuscular complications (fracture) that were secondary to the tetanus

spasms, corresponding to 9.6% of the sample.

The majority of the patients were discharged from the hospital. The median lengths of the ICU and hospital stays were 23 (4–84) days and 33 (9–85) days, respectively.

Two of the patients died. There was no association between the length of the ICU stay and lethality ($p=0.4$). One of the patients who died was 64 years old, and the other was 76 years old. In contrast, the mean age of the surviving patients was 45.6 years (5 to 72 years old). Although this difference may suggest a association between lethality and age, the correlation between these metrics was not statistically significant ($p=0.06$) (Table 2).

Our sample was composed of only four women, two of whom died. Despite the small number of women, there was a significant association between gender and prognosis ($p=0.03$).

The vast majority of the patients developed a generalized descending pattern of tetanus (17 patients). Despite theoretically being more severe, this pattern was not associated with a poor prognosis ($p=0.65$). No significant association was observed between the portal of entry of the infection and lethality.

The APACHE II severity scores were significantly different between the survivors and the patients who died ($p=0.04$). However, this score was undetermined for one of the two patients who died. With respect to the Veronesi tetanus scale, the difference in severity was more consistent; both of the patients who died were classified as exhibiting a very severe infection ($p=0.03$).

There were no significant differences between the occurrence of cardiovascular complications and age ($p=0.09$) or gender ($p=0.67$). However, there was a strong association between the Veronesi classification ($p=0.013$) and the length of the ICU stay ($p=0.009$) with the development of cardiovascular complications (Table 3).

Table 3 – Clinical comparison with respect to the development of cardiovascular complications in patients with tetanus

Characteristic	No cardiovascular complication (N=10)	Cardiovascular complication (N=11)	Global (N=21)	p value
Gender (male)	8 (80)	9 (81.8)	17/21 (81)	0.67*
Age (years)	42.5 ± 15.9	55 ± 16.5	47.8 ± 17.5	0.09#
Portal of entry				
Upper limb	1	1	2	0.62 ^z
Lower limb	9	9	18	
Abdominal	0	1	1	
Not available	1	0	1	
Incubation period (days)	9 (1-15)	7 (6-14)	8 (1-15)	0.93#

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Table 3 – Continuation

Characteristic	No cardiovascular complication (N=10)	Cardiovascular complication (N=11)	Global (N=21)	p value
Mean onset period (hours)				
< 48	1	1	2	0.78 [‡]
48-72	1	4	5	
> 72	4	5	9	
Open	1	1	2	
Unknown	3	0	3	
Clinical presentation				
Descendent generalized	7	10	17	0.40 [‡]
Ascendant generalized	2	1	3	
Localized	1	0	1	
APACHE II				
< 13	10	8	18	0.47 [‡]
> 13	0	2	2	
Undetermined	0	1	1	
Veronesi classification				
Mild	6	1	7	0.013 [‡]
Severe	4	5	9	
Very severe	0	5	5	
Length of ICU stay (days)	10 (4-30)	33 (4-84)	23 (4-84)	0.009 [§]

APACHE - Acute Physiological Chronic Health Evaluation; ICU – intensive care unit. The results are expressed as the number (percentage), the mean ± standard deviation or the median (minimum-maximum). *Fisher Exact Test; † Student's t-test; ‡ Chi-square; § Mann-Whitney test.

DISCUSSION

This study presents the characteristics of patients who developed tetanus in São Paulo State, Brazil. Adults were more likely to be infected (mean age=47.8 years), as were males (81.8%) and those from the countryside or the coast (72.7%). These results demonstrate that active men from outside of the capital in São Paulo State are vulnerable to tetanus, particularly those infections that are secondary to a failure in workplace prevention. Corroborating this suspicion, we observed that the majority of patients had never been vaccinated against the disease (81%).

Following the trauma, only 54.5% of the patients sought medical care. Unfortunately, none of patients who sought medical care following the injury received adequate treatment, which could have prevented the disease. This finding is evidence of a failure of primary care in the prevention of post-traumatic tetanus.

Respiratory problems were the most commonly observed ICU complications (61.9%), followed by secondary infections (59.1%), cardiovascular (52.4%), and renal complications (23.8%).

Although we included dysautonomy as a cardiovascular complication rather than considering it to be part of the clinical course of tetanus, this event occurred in only

one patient and did not greatly impact our analysis. Pressure ulcers were the most frequent cardiovascular complication, followed by arrhythmias. The development of severe muscular lesions with high levels of creatine phosphokinase and renal failure were associated with hypervolemia and acute pulmonary edema. The patients with longer ICU stays exhibited a significant increase in cardiovascular complications (p=0.009) and a more severe disease according to the Veronesi classification (p=0.03). Twenty-four-hour electrocardiography monitoring is important for the detection of arrhythmias; otherwise, some arrhythmias can be misdiagnosed.⁽²⁰⁾

The mortality of tetanus patients admitted to the ICU was 9.1% (2/22 patients), a rate that is comparable to those observed in higher quality ICUs in developed countries. This fact is likely attributable to the level of knowledge and specialization of our multidisciplinary team in managing tetanus and to advances in critical care resources. Although 33.3% (7/21 patients) were classified as exhibiting mild cases, early adequate therapeutic intervention and monitoring in the ICU were fundamental in avoiding the natural progression of the symptoms.

The low mean APACHE II severity score of the tetanus patients upon admission reflects the benign character of the disease during the onset period. Both female gender

($p=0.03$) and the Veronesi tetanus classification ($p=0.03$) were risk factors for lethality. More severe infections in women have been noted, and female gender is associated with a less evident clinical manifestation.⁽²¹⁾ Older women present disproportionately severe peripheral muscle spasms and laryngeal spasms, likely because of the flaccidity of the abdominal and paravertebral muscles; these patients therefore require special attention.

Older patients tend to have a poor prognosis for tetanus.⁽²¹⁾ However, in our sample, age was not an independent significant risk factor for tetanus lethality or for the development of cardiovascular complications.

Our study has some limitations. First, this is a retrospective study, and certain information was not available in the medical records. Furthermore, the small number of patients limited the power of the multivariate analyses.

CONCLUSION

The present study demonstrates that several actions need to be taken to improve tetanus prophylaxis in São Paulo State, Brazil, particularly with respect to workplace and post-traumatic tetanus prevention. In addition to appropriate optimization of myorelaxation to prevent muscular lesions and advances in critical care resources, the adequate prevention and management of cardiovascular complications can be essential in reducing the length of the ICU stay and in promoting the quality of life of patients with tetanus.

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RESUMO

Objetivo: Apesar do declínio em sua incidência, o tétano ainda é uma doença negligenciada nos países em desenvolvimento, permanecendo como causa importante de morbidade

e mortalidade. Atualmente, com o aperfeiçoamento dos cuidados de terapia intensiva, torna-se importante conhecer melhor as complicações dessa grave condição. Este estudo visa avaliar a letalidade e complicações cardiovasculares e osteomusculares de pacientes com diagnóstico de tétano internados em unidade de terapia intensiva e os fatores associados ao pior prognóstico.

Métodos: Este foi um estudo retrospectivo realizado por meio da análise de prontuários médicos de pacientes com diagnóstico de tétano admitidos em unidade de terapia intensiva, de janeiro de 2000 a dezembro de 2001. Foram colhidas informações demográficas, clínicas e laboratoriais por meio de um questionário padrão. São descritas as variáveis relacionadas à letalidade, complicações cardiovasculares e osteomusculares.

Resultados: No período do estudo foram internados 22 pacientes com tétano, sendo 81,8% homens, com média de idade de 47,8 anos. O tétano era associado a atividades profissionais em 54,5% dos casos. A maioria dos pacientes desenvolveu a forma generalizada da doença (20 pacientes); em 81% dos casos, os pacientes nunca haviam recebido vacina antitetânica ou desconheciam sua situação vacinal. Após o ferimento, nenhum paciente recebeu profilaxia passiva apropriada e apenas dois foram submetidos a debridamento cirúrgico do foco, enquanto seis pacientes receberam antibioticoterapia. Onze pacientes (52,4%) desenvolveram alguma complicação cardiovascular. Úlcera de pressão foi a complicação cardiovascular mais frequente (38,1%), seguida por arritmias (28,6%). Dois pacientes desenvolveram fraturas ósseas secundárias ao espasmo tetânico, correspondendo a 9,6% da amostra. A letalidade do tétano foi de 9,1%. Escore de APACHE II alto e forma gravíssima na classificação de tétano de Veronesi se associaram a maior risco de óbito ($p=0,04$ e $0,03$, respectivamente). A classificação de Veronesi também se associou ao risco de complicações cardiovasculares ($p=0,013$) assim como a um maior tempo de permanência na unidade de terapia intensiva ($p=0,009$).

Conclusão: O presente estudo demonstra falha na atenção primária à saúde em termos de cobertura vacinal e profilaxia do tétano pós-traumático em adultos. Apesar do aprimoramento do suporte intensivo, as complicações cardiovasculares ainda são frequentes nesses pacientes. Indivíduos com alto escore APACHE II e forma clínica gravíssima precisam ser cuidadosamente monitorizados devido ao maior risco de óbito e de complicações cardiovasculares.

Descritores: Tétano/complicações; Letalidade

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