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# Changes in severe accidental tetanus mortality in the ICU during two decades in Brazil

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**Abstract** *Introduction:* Tetanus is still a significant health hazard in developing countries, with high associated mortality. *Objective:* Describe the management of patients with severe tetanus in intensive care units (ICUs), in two different periods. *Setting:* ICUs of two general hospitals. *Design:* Concurrent cohort study. *Methods:* Follow-up of all patients hospitalized with the diagnosis of severe tetanus in the ICUs from October 1981 to March 2001. We collected data prospectively, regarding the site of injury, clinical features, frequent clinical and infectious complications, concomitant illnesses, and mortality. The patients were divided into two groups according to the treatment protocol used; before 1993 and after 1993. *Results:* There were 126 patients in group 1 (93 males) with a mean age of 39.0±18.8 years. There were 110 patients in group 2 (95 males) with a mean age of 48.4±17.8 years. Incubation period, onset period, and symptomatic period were higher in group 2 ($P \leq 0.02$). The duration of neuromuscular junction blockade, benzodiazepine administration, mechanical ventilation, and ICU stay were longer in group 2, $P<0.001$. Infectious complications were more frequent in group 2 ($P<0.001$). The mortality rate in group 1 was 36.5% and in group 2, 18.0% ($P=0.002$). Mortality was directly associated with symptomatic period, acute renal failure cardiac arrest and hypotension, and inversely associated with onset period in the multivariate analyses. *Conclusions:* The reduced mortality in severe accidental tetanus patients in group 2 is probably related to advances in ICU management, despite the higher incidence of infectious complications, which are probably related to the longer ICU stay.

**Keywords** Tetanus · Accidental tetanus · Tetanus mortality

## Introduction

Tetanus is an intoxication of the central nervous system caused by tetanospasmin, a toxin produced by the anaerobic bacillus, *Clostridium tetani*. It is characterized by persistent tonic spasms, with violent exacerbation and clinical symptoms [1, 2]. Uncommon in developed countries, due to effective widespread immunization, preventive measures taken with wounds, and the use of immunoglobulin, it remains a significant health hazard in developing countries. About 1,000,000 cases/year of tetanus are thought to occur in the world [2]. In Brazil, the overall incidence of accidental tetanus decreased between the early 1980s and the late 1990s, from 1.8 to 0.8/100,000. In Rio Grande do Sul, a southern state in Brazil, the incidence decreased, during this period, from 2.05 to 0.39/100,000 [3], with a mortality rate ranging between 19% and 32% [4, 5].

The temporal development of the symptoms of tetanus is of great prognostic significance. Regardless of the clinical type of tetanus, shorter incubation and onset periods indicate poorer prognosis. The incubation period is

the time from spore inoculation to the initial symptom of tetanus. This period reflects the time needed for germination of the spores, proliferation of the bacteria, and the production of tetanospasmin. The onset period – the time from the first symptom to the first muscular spasm – reflects the progression of neurological manifestations caused by the tetanus toxin. The toxin is transported in the neurons into the central nervous system, which takes from 10–14 days. Recovery then begins, usually requiring about 4 weeks. With no antitoxin, the disease persists for as long as tetanospasmin is produced [1, 2]. The progression of clinical symptoms of tetanus, such as respiratory failure and autonomic instability, are associated with high morbidity and mortality in the early hospitalization period. Later in the course of the disease, death results from complications of autonomic instability or prolonged ICU exposure [6, 7]. Our objectives are to report the experience of managing patients in the ICU with severe accidental tetanus, in two different periods, regarding clinical characteristics, frequent clinical and infectious complications, concomitant illnesses, and changes in mortality.

## Patients and methods

### Study population

All patients admitted in the ICUs of two general hospitals (Hospital Nossa Senhora da Conceição and Hospital de Clinicas de Porto Alegre), with the diagnosis of severe tetanus, from October 1981 to March 2001, were consecutively enrolled in this study after implementation of a specific protocol. The data were prospectively collected and reviewed every 2 years. The ethics committees of both hospitals approved this research.

Ablett's scale classifies tetanus into mild, moderate, severe, and very severe. All patients in the study had the diagnosis of severe tetanus established by clinical characteristics based on the modified Ablett's scale: marked rigidity, frequent generalized spasms, dysphasia, respiratory involvement or apnea [2, 8]. The study variables included: age, sex, injured area, periods of the disease and temporal development of symptoms, clinical characteristics, clinical and infectious complications, mortality rate, and treatment.

Temporal development of symptoms was analyzed with the following variables: incubation period (IP) – the period that extends from the time of spore inoculation to the first symptom; onset period (OP) – the time from the first symptom to the first reflex spasm; symptomatic period (SP) – the time from the first symptom to the last reflex spasms, encompassing the onset period, the times of disease progression and recovery, until complete remission of spasms. Recovery is tested by the absence of spasm recurrence, after decreasing doses of curare and benzodiazepines.

During the first period of study all patients were handled according to standard procedures for tetanus, including débridement and subsequent care of lesions, tracheotomy at the first 24 h after the diagnosis of severe tetanus, antibiotics (penicillin or metronidazole), immunization with tetanus toxoid and immunoglobulin (3,000–5,000 UI), sedatives (diazepam, 40–240 mg/24 h), and neuromuscular blocking agents (pancuronium EV, “as needed” to control spasms). Treatment of hyperadrenergic activity included: beta-blockers as first choice (propranolol, 10–40 mg, VO/24 h) or morphine (4 mg subcutaneous until 4/4 h) as needed; clonidine (0.75–0.30 mg) and chlorpromazine (50–300 mg/24 h) was occasionally used as adjunct medication, as needed; enteral nutrition by nasogastric tube (hypercaloric and hyperproteic); prophylaxis of thromboembolism with heparin (5000 UI SC 12/12 h); and use of anti-infective agents for infectious complications. Bird Mark 7 (Bird, USA or Takaoka, Brazil) was used for mechanical ventilation, in a pressure-cycled mode. Non-invasive EKG monitoring was performed.

The protocol was modified at the end of 1993 with: a reduction of the dose of immunoglobulin (500 IU); an increased dose of diazepam (240–800 mg EV); morphine as the first choice for hyperadrenergic activity (10–40 mg/24 h, in intravenous continuous infusion EV), followed by clonidine and chlorpromazine, as needed; enteral nutrition by nasoenteric tube, oriented by nutritional support; early physiotherapy; substitution of older ventilators by more modern ones (Bird 8400, Bird, USA; Servo 900 or Servo 300, Siemens, Germany) using pressure control or volume control, with PEEP =5, which was modified according to the lung compliance; and better continuous non-invasive monitoring (66S model, Hewlett-Packard, USA), that includes EKG, arterial pressure, and oxygen saturation. APACHE II was used as severity score for ICU tetanus patients. Other measures were maintained as in the first protocol. In order to compare the two periods with different management strategies, we divided the patients into two groups: group 1 – patients enrolled from October 1981 to December 1993; group 2 – patients enrolled from January 1994 to March 2001.

### Statistical analysis

Continuous variables were described as means and standard deviations; frequency tables and proportions described categorical variables. The two groups were compared regarding clinical variables, mortality, and treatment with the use of Student's *t*-test for continuous and normally distributed variables, the Mann Whitney test for asymmetrical variables, and chi-square for categorical variables. For all comparisons, a significance level of 0.05 was used. Logistic regression was performed to analyze differences in mortality between groups, controlling for the group characteristics that showed significant differences in univariate analyses. Additionally, risk factors for mortality were studied within each group. Relative risks and 95% confidence intervals were calculated for these risk factors.

## Results

Group 1 consisted of 126 patients: 93 males (74.6%) and 33 females (25.4%) with a mean age of 39 (±18.8) years. Group 2 consisted of 110 patients: 95 males (86.4%) and 15 females (13.6%), with a mean age of 48.5 (±17.8) years, $P$=0.03 and APACHE of 7.09±4.70. Only three patients in each group knew about previous complete tetanus immunization.

Table 1 compares the temporal development of the symptoms and the periods of use of curare, benzodiazepines, mechanical ventilation, and ICU hospitalization in survivors and in all patients. These periods were significantly greater in group 2.

### Concomitant illnesses

Hypertension, diabetes mellitus, and coronary heart disease occurred equally in both groups; however, in

**Table 1** Characteristics of groups considering all patients and survivors. *P* value comparison between group 1 and group 2 (*t*-test). (*IP* incubation period, *OP* onset period, *SP* symptomatic period, *BENZOP* benzodiazepine period, *CURP* curare period, *MVP* mechanical ventilation period, *ICUP* intensive care period)

| | All patients | | | Survivors | | |
|---|---|---|---|---|---|---|
| | Group 1 (*n*=126 | Group 2 (*n*=110) | *P* value | Group 1 (*n*=90) | Group 2 (*n*=90) | *P* value |
| IP (days ± SD) | 7.9±4.3 | 9.4±5.7 | 0.02* | 8.1±4.6 | 9.9±6.1 | 0.045* |
| OP (days ±SD) | 2.3±3.1 | 3.2±2.6 | 0.02* | 2.3±2.9 | 3.2±2.5 | 0.038* |
| SP (days ±SD) | 24.7±13.2 | 38.0±14.8 | <0.001* | 29.8±11.9 | 40.1±13.4 | <0.001* |
| BENZOP (days ±SD) | 23.4±13.0 | 36.1±14.6 | <0.001* | 28.4±11.8 | 38.9±13.2 | <0.001* |
| CURP (days ±SD) | 16.8±10.6 | 29.0±14.3 | <0.001* | 19.4±10.6 | 30.4±13.9 | <0.001* |
| MVP (days ±SD) | 18.4±10.9 | 36.6±15.7 | <0.001* | 18.4±10.9 | 36.6±15.7 | <0.001* |
| ICUP (days ±SD) | 23.2±12.3 | 42.8±17.8 | <0.001* | 27.8±10.9 | 45.7±15.7 | <0.001* |

*Statistical significance between groups

**Table 2** Injury location and types

| | Group 1 (*n*=126) | | Group 2 (*n*=110) | |
|---|---|---|---|---|
| | *n* | (%) | *n* | (%) |
| Locations: | | | | |
| Lower limbs | 77 | (61.1) | 71 | (64.5) |
| Upper limbs | 26 | (20.6) | 20 | (18.8) |
| Head | 8 | (6.3) | 6 | (5.4) |
| Trunk | 3 | (2.3) | 1 | (0.9) |
| Uterus | 2 | (1.6) | 0 | (0) |
| Not identified | 10 | (7.9) | 12 | (10.9) |
| Types: | | | | |
| Laceration wounds | 85 | (67.4) | 66 | (60) |
| Puncture wounds | 15 | (12.0) | 8 | (7.3) |
| *T penetrans* | 4 | (3.2) | 9 | (8.2) |
| Trauma: car accident | 4 | (3.2) | 7 | (6.3) |
| Gunfire | 3 | (2.3) | 3 | (2.7) |
| Intravenous drug abuse | 2 | (1.6) | 5 | (4.5) |
| Infection (abortion =2, foot =1) | 3 | (2.3) | 0 | (0) |

group 2, there were more patients with alcoholism (27/110 –24.5%) and chronic obstructive pulmonary disease (31/110–28.2%) than in group 1 (12/126–9.5% and 9/126–7.1%, respectively), $P<0.005$.

## Injury sites

The sites of injury are summarized in Table 2. There were no statistical differences between the frequencies of injury in both groups. The most common type was laceration followed by puncture wounds. In Brazil, chigger bites (*Tunga penetrans* skin injury), is one of the entry sites for tetanus spores. Tetanus in trauma patients was observed in both groups, with a higher incidence in group 2 (9.0%) than in group 1 (5.4%). In group 1, two patients developed tetanus after inducted abortions.

**Table 3** Autonomic instability, and clinical and infectious complications rate. *P* value comparison between group 1 and group 2 (chi-square test). [*AI* autonomic instability (blood pressure instability plus arrhythmia), *δ* arrhythmias other than sinus tachycardia, *CPA* cardiopulmonary arrest, *ARF* acute respiratory failure, *TET* troubles with tube or ventilators, *Pneumo/med* pneumothorax or pneumomediastinum, *Neuro dysfunction* neurological dysfunction, *NS* not significant]

| Complications | Group 1 (*n*=126) | | Group 2 (*n*=110) | | *P* value |
|---|---|---|---|---|---|
| | *n* | % | *n* | % | |
| AI | 98 | (77.8) | 89 | (80.9) | NS |
| CPA | 56 | (44.4) | 17 | (15.5) | <0.001* |
| Arrhythmias (δ) | 20 | (15.9) | 51 | (46.6) | <0.001* |
| Hypertension | 10 | (7.9) | 58 | (52.7) | <0.001* |
| Hypotension | 32 | (25.4) | 38 | (34.5) | NS |
| Clinical complications: | | | | | |
| ARF | 126 | (100) | 110 | (100) | NS |
| Atelectasis | 24 | (19) | 18 | (16.4) | NS |
| Renal Failure | 5 | (4.0) | 7 | (6.4) | NS |
| TET | 10 | (7.9) | 9 | (8.2) | NS |
| Pneumo/med | 22 | (17.5) | 4 | (3.6) | 0.001* |
| Neuro dysfunction | 12 | (9.5) | 0 | (0) | <0.001* |
| Infectious complications: | | | | | |
| Respiratory tract | 105 | (83.3) | 105 | (95.5) | 0.005* |
| Urinary tract | 46 | (36.5) | 64 | (58.2) | <0.001* |
| Cutaneous infectious | 19 | (15) | 9 | (8.2) | NS |
| Catheter infectious | 1 | (0.8) | 30 | (27.3) | <0.001* |

*Statistical significance between groups

## Autonomic instability

Heart rate instability was present in all patients. Blood pressure instability associated with arrhythmias (including sinus tachycardia) occurred in both groups: 77.8% in group 1 and in 80.9% in group 2 (NS). However, each group manifested autonomic dysfunction differently: hypertension and arrhythmias (other than sinus tachycardia) were less frequent in group 1 than in group 2. On the other hand, cardiac arrest was more frequent in

**Table 4** Relative risk of mortality for specific variables related to autonomic instability and complications in both groups in univariate analysis. (*CI* confidence interval, *RR* relative risk, *δ* no death, *δδ* all patients with respiratory tract infection)

| | Group 1 (*n*=126) RR (95% CI) | Group 2 (*n*=110) RR (95% CI) |
|---|---|---|
| Autonomic instability: | | |
| Arrhythmia | 2.56 (1.74–3.79) | 1.41 (0.64–3.14) |
| Hypertension | 1.74 (0.99–3.06) | 0.9 (0.41–1.98) |
| Hypotension | 2.94 (1.94–4.45) | 5.68 (2.24–14.45) |
| Cardiac arrest | 6.96 (3.38–14.36) | 10.16 (4.65–21.62) |
| Complications: | | |
| Pneumothorax/ pneumomediastinum | 0.85 (0.44–1.64) | 2.90 (1.01–8.55) |
| Cannula occlusion | 2.44 (1.63–3.66) | δ |
| Respiratory tract infection | 0.46 (0.3–0.69) | δδ |
| Urinary tract infection | 0.42 (0.22–0.80) | 0.39 (0.17–0.89) |
| Acute renal failure | 2.30 (1.40–3.81) | 3.68 (1.68–8.06) |

group 1 than in group 2 (Table 3). In the treatment of autonomic dysfunction, no patient received propranolol in group 2 but morphine was used in all patients in this group.

### Clinical and infectious complications

The incidence of pneumothorax/pneumomediastinum and neurological dysfunction was greater in group 1 than in group 2, but the incidence of respiratory, urinary tract, and catheter infections was higher in group 2 (Table 3).

### Mortality

The mortality rate in group 1 was 36.5% and in group 2, 18.0% ($P$=0.002). In group 1, there was a significant association of mortality, with older patients, autonomic instability (arrhythmia, hypotension, cardiac arrest), cannula occlusion, acute renal failure, and respiratory and urinary tract infections.

In group 2, mortality was associated with autonomic instability, represented by hypotension and cardiac arrest, pneumothorax/pneumomediastinum, and acute renal failure. (Table 4).

The duration of SP was inversely related to the risk of death in both groups: group 1, non-survivors 16.0± 10.7 days vs survivors 29±11.9 days ($P$<0.001); group 2, non-survivors 28.6±17.6 days vs survivors 40.2±13.4 days ($P$<0.001).

There was no association of mortality with diazepam doses used in either groups, although the doses were higher in group 2 (236.61±52.62 mg/24 h versus 594.86±242.95 mg/24 h), $P$<0.005. The doses of pancuronium used in group 1 were higher than in group 2 (45.45±17.0 mg/24 h versus 38.09±15.23 mg/24 h), $P$<0.02, but there was no association with mortality in any group. Lengths of diazepam and curare use were associated with mortality in both groups.

**Table 5** Variables associated with mortality in all patients in multivariate analyses. Group 2 is considered the control group in this model. (*OR* Odds ratio, *IP* incubation period, *OP* onset period, *SP* symptomatic period)

| Variable | *P* | OR | CI (95%) |
|---|---|---|---|
| Group (1) | 0.675 | 1.381 | 0.305–6.247 |
| Age | 0.682 | 0.994 | 0.965–1.024 |
| IP | 0.343 | 1.065 | 0.935–1.211 |
| OP | 0.027 | 0.842 | 0.723–0.981 |
| SP | 0.000 | 1.111 | 1.0570–1.168 |
| Hypotension | 0.036 | 3.523 | 1.086–11.425 |
| Cardiac arrest | 0.000 | 26.539 | 7.845–89.777 |
| Acute renal failure | 0.012 | 3.523 | 1.086–11.425 |
| Infections | 0.159 | 5.080 | 0.530–48.733 |

All patients who died developed autonomic dysfunction during the course of their disease. In group1 39/46 (84.7%) patients had cardiac arrest, 23/46 (50%) hypotension, and 14/46 (30.4%), arrhythmia. In group 2 cardiac arrest occurred in 7/20 (35%) patients, hypotension in 11/20 (55%), and arrhythmia in13/20 (65%). This was not always the cause of death. Analyzing all causes of death, in group 1, 45.6% of deaths were due to autonomic instability, especially during the first and second weeks of hospitalization (9.5±7.3 days). During the third week of hospitalization, 26% of deaths were due to difficulties with respiratory probes including cannula occlusion, ventilator disconnection, pneumothorax, and pneumomediastinum. During the fourth week of ICU stay (26.9±10.9 days), 23.9% of deaths were caused by multiple organ dysfunction, secondary to infections. One death was caused by malignant hyperthermia and one by pulmonary embolism. In group 2, most deaths were due to multiple organ dysfunction or septic shock (65%) occurring during the seventh and eighth weeks of ICU stay (40.0±19.0 days), and 35% to autonomic instability in the first 2 weeks of hospitalization (11.1±4.1 days), as in group 1. In group 2, there were no deaths due to problems with respiratory probes.

The multivariate analyses showed that duration of symptomatic period, cardiac arrest, and hypotension were significantly associated with mortality and inversely associated with onset period, controlling for the following variables: period of study, age, IP or infection. Hypertension, diabetes mellitus, coronary heart disease, arrhythmias, and doses of diazepam and pancuronium were not significant and they were not included in the final model of this analyses (Table 5).

## Discussion

In our study we observed a reduced mortality in severe accidental tetanus over two decades, even though group 2

was older, with a higher duration of symptomatic period, benzodiazepine and neuromuscular junction blockade, ICU stay, and infectious complications than group 1. Mortality was directly associated with symptomatic period, acute renal failure, hypotension, and cardiac arrest and inversely associated with onset period in the multivariate analyses. The decreased mortality in the second period probably reflects improvements in ICU resources and treatment of autonomic instability.

The mortality rate from accidental tetanus ranged from 40% to 60% in the 1980s [5, 10]. In the 1990s, the mortality rate among patients with severe tetanus who required mechanical ventilation, ranged from 18% to 29.5% [9, 11, 12, 13]. Mortality in the different periods of our series was similar to the reported rates: 36.5% in group 1 and 18% in group 2.

Cardiac arrest occurred in 44.4% of the patients in group 1 and in 15.5% of the patients in group 2, or put in another way, group 1 had 26.5 times more probability of cardiac arrest than group 2. This was caused by autonomic instability and by problems associated with respiratory probes. The high incidence of problems related to mechanical ventilation observed in group 1, was associated with pressure-cycled mode, old non-alarmed respiratory probes (cannula obstruction, barotrauma, disconnected respiratory probe), and higher pressures and volumes used. In group 2, mechanical ventilation used pressure- and volume-control mode with lower volumes; physiological PEEP was altered as necessary. No cardiac arrest associated with mechanical ventilation occurred in group 2. These differences were similar to the series of Trujillo in the 1980s [7] and Gregorakos in the 1990s [12].

Autonomic dysfunction with blood pressure instability was observed in about 80% of the patients in both groups, and was not different from other series [13, 16]. The poor prognosis associated with this condition was more commonly observed in group 1, in which more deaths were caused by autonomic instability (45.6%) than in group 2 (35%). This difference may reflect improvements in arrhythmia management, better resuscitation, more cardiovascular stability with use of morphine, and decreased dose of pancuronium in group 2. The higher incidence of hypertension and arrhythmia detected in group 2 was probably related to the use of modern continuous non-invasive pressure and EKG monitoring, allowing the detection of tachyarrhythmias and bradyarrhythmias that forecast cardiac arrest. Although no therapeutic regimens have proved to be universally effective in the treatment of hyperadrenergic activity, some have been proposed, such as reposition of volume, deep sedation with higher doses and longer duration of treatment with benzodiazepines [17, 18, 19], use of chlorpromazine, β-adrenergic blocking agents, morphine, and clonidine [20, 21, 22, 23]. In our study we tried to improve this treatment by using higher doses of diazepam and lower doses of curare, given that pancuronium could worsen tachycardia and hypertension [24]; avoiding propranolol (used in group 1), whose use can be related to sudden death, hypotension, and severe pulmonary oedema [25, 26, 27]; using morphine (used in group 2), which is related to better cardiovascular stability [24, 28].

The higher incidence of infectious complications in group 2 may be explained by the prolonged exposure to the ICU environment, mechanical ventilation, and by the use of indwelling catheters and other invasive procedures [7]. We speculate that the use of higher doses of diazepam in group 2 could have accounted for a longer ICU stay, since the sustained infusions of sedatives were associated with statistically longer duration of mechanical ventilation and length of stay [29, 30, 31].

All patients in our study were classified as severe tetanus by Ablett's scale, although incubation and onset periods – even if shorter in group 1 – were short in both groups, characterizing, as in other studies, the severity of the disease [1, 5, 9]. Even though patients in group 2 were older than those in group 1, with more alcoholism and chronic pulmonary disease, the mortality was lower than group 1. We cannot compare severity scores of critically ill patients between groups, such as APACHE, because this routine was implemented in the ICU since 1993.

Differences in age between each period could be related to increasingly widespread practice of vaccination, better wound care for trauma patients, and social and cultural changes (mechanization of agriculture and better health education), since the 1980s [1, 11]. Gender distribution, with male predominance in both groups, are the same as described in other countries. This is attributed to greater exposure of men to minor trauma, with infection, at work or outside of work [1, 14, 15]. The frequency of different injury sites, as well as of undetected injuries, was similar to that described in the literature. Intravenous drug users were more common in group 2 than in group 1, as its practice has increased [1, 9].

The use of immunoglobulin 500 IU was as effective as the commonly recommended dose of 3,000–5,000 IU in a retrospective study [32]. In our study, the use of a smaller dose of immunoglobulin in group 2 seemed safe, once there were no differences in incidence of autonomic instability and clinical complications of severe tetanus in both groups. However, the actual role of immunoglobulin used after clinical tetanus is already established is still controversial.

In conclusion, tetanus is an entirely preventable disease but it continues to have high morbidity and mortality. The reduced mortality in group 2 is probably related to advances in ICU resources and to better treatment of autonomic dysfunction. In any case, this study is a good example of the paradox of health with the introduction of high technological resources. Mortality is reduced but, on the other hand, costs increase with the duration of ICU stay. Preventive vaccination remains the most important strategy to avoid tetanus.

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