

SEVERE TETANUS IN INTENSIVE CARE UNIT: ABOUT 20 CASES

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ABSTRACT

Introduction: Tetanus is a non-contagious, not immunizing, infectious disease. In developed nations, effective immunization programs have led to a significant decrease in its incidence, making it a rare pathology only seen sporadically. In Morocco, the disease remains a major health problem leading to multiple deaths every year.

Materials and Methods: This is a five-year period retrospective study, including all cases of severe tetanus hospitalized in the two intensive care units (ICU); A1 and A4, at the Hassan II^d teaching hospital.

Results: Twenty cases were included in this study. The mean age of our sample was 50 years old. The sex ratio was 5.6 M / F. None of our patients had undergone a proper vaccination. 90% of our patients presented paroxysms when first admitted to the ICU. All had a lockjaw. 13 patients were intubated. Twelve patients received injectable midazolam. Five patients required continuous curarisation. All patients received serum therapy and 16 of whom were put on metronidazole. Eleven patients died.

Discussion and conclusion Tetanus still prevails in third-world countries. In Morocco, the disease targets young males as opposed to developed countries. Generalized tetanus treatment is complex and requires hospitalization in intensive care and close monitoring of the patient. Its mortality is still high. Mortality risk factors in our study included: advanced age, high dosage of CRP, wound depth, kidney failure, neuro-vegetative disorders and sepsis.

Key words: Intensive care unit; Tetanus; Trismus; Prognosis; Mortality.

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INTRODUCTION

Tetanus is a severe acute toxigenic infection caused by tetanospasmin, an extremely potent protein toxin produced by the *Clostridium tetani* cell. The contamination can occur through open cuts, even minor ones, such as insects' bites or abrasions. The positive diagnosis is an exclusively clinical one. There are two types of tetanus: generalized tetanus, characterized by trismus, hyper-reflection and generalized muscle contractions, and localized tetanus, a benign condition that only affects muscles around the entry site. Tetanus, although lethal, can be avoided through vaccination. The tetanus vaccination has been part of the National Immunization Program (NIP) in Morocco since 1963. New cases however, are still encountered every year despite vaccination. This disease—very

much still a major health problem in developing countries - has been almost eradicated in developed countries, and has been poorly represented in the scientific literature over the past five years, only through a handful of anecdotal cases by authors not used to this type of illness. An update on this serious disease became necessary. We decided to study the epidemiological, clinical, therapeutic and prognostic aspects of all cases of generalized tetanus admitted to our hospital.

MATERIALS AND METHODS

We have conducted a longitudinal descriptive-analytic retrospective study, in the two Intensive Care Units of Hassan II^d University Hospital Center at Fez, over a period of 6 years, from January 2009 to December 2015, including all patients

hospitalized for severe generalized tetanus older than 16 years old. The diagnosis of severe tetanus was clinical. We created a data collection form specific to the information we were going to need in our study and collected all the necessary data from computerized medical files. We used the SPSS 20 software for the statistical analysis of demographic, clinical, paraclinical, therapeutic and evolutive parameters.

As for the descriptive part of our study, the quantitative variables were expressed by mean and standard deviation, and the qualitative variables were expressed by percentage. For the analytical part, a univariate analysis was performed by comparing the means and percentages respectively using Student's t-test and Pearson's chi-square test (χ^2). The result was considered significant when $p < 0.05$.

RESULTS

We collected 20 cases of severe generalized tetanus over the studied period. The average age was 50 (with extremes of 17 and 87). The sex ratio was 5.6H / F (85% were male). Only 4 of our patients had associated co-morbidities: Hypertension, Biermer's disease, pulmonary tuberculosis and ischemic heart disease. Only one patient had a history of renal nephrolithiasis surgery 4 years before the tetanus episode. None of our 20 patients were correctly vaccinated. We did not use the Tetanus Quick-test in our study due to its unavailability in Morocco.

The Clostridium tetani's entry site was identified in 17 patients: 14 patients had a single wound (70%) whereas 3 patients had multiple wounds. No wound could be identified in 3 of our patients (15%). 8 patients had puncture wounds and 3 patients had dermal abrasions. 13 patients had deep wounds (76%) whereas 4 patients suffered superficial ones (24%). 12 patients had clean wounds and 5 patients had infected ones. Fourteen wounds were situated on the lower limbs, one on the abdomen and two on the upper limbs.

The average incubation period was 8 days (with extremes of 3 and 17 days), and patients presented to the emergency room 3.3 days on average after the onset of clinical symptomatology.

At admission, all patients had a trismus. 90% of patients had paroxysms. These paroxysms were generalized immediately in 16 patients, and occurred on average 5 times per day. Vegetative signs were present in 6 patients. Five patients were febrile upon their admission to the intensive care unit, and ten had an elevated white cell account. 71 patients had high CRP levels. At admission, only one of our patients had a Dakar score ranging

between 5 and 6, two patients had a score of 4 and 55% of patients had a score of 2-3.

All of our patients received diazepam, 12 received intravenous midazolam using electric syringe, and five patients were treated with curare for paroxysms. Respiratory management depended on the degree of distress: 7 patients received nasal or masked oxygen therapy alone. Of the thirteen patients who were intubated, 6 had to be tracheotomized. A central venous catheter was placed in 8 patients, 7 of whom needed the use of vasoactive drugs. All patients received a 500 IU injection of anti-tetanus serum and a tetanus toxoid booster upon admission. Sixteen patients received metronidazole and four patients received penicillin G alone. Fifteen patients benefited of enteral feeding whereas 25% of patients in our series (n= 5) received parenteral nutrition.

The most frequent complications were:

- Pressure ulcers : 7 patients
- Pneumopathies: 6 patients
- Neurovegetative disorders: 6 patients
- Bacteremia: 5 patients
- Acquired Neuromuscular disorders:4 patients
- Urinary infection: 3 patients
- Osteo-articular complications: 2 patients
- Scrotal abscess: 1 patient.

The average duration of stay in the ICU was 16 days (with extremes of 2 and 42 days). Eleven patients (55%) died:

- 5 patients died of septic shock associated with multiple organ failure: 4 from complications of healthcare associated pneumonia (HCAP) and one from scrotal abscess.
- 6 patients died from neurovegetative disorders.

In univariate analysis, the risk factors for mortality in our study were:

- Advanced age (p = 0.008)
- High CRP levels (p = 0.021)
- Wound depth (Superficial) (p = 0.05)
- Renal failure (p = 0.03)
- Neuro-vegetative disorders (p = 0.012)
- Bacteremia (p = 0.03).

Tables I and II sum up the qualitative and quantitative variables studied in our series. We could not conduct a multivariate analysis due to the small size of our sample and the heterogeneity of its distribution.

Table I: Quantitative prognostic variables in our study

Quantitative variables	p (Chi 2)
Age	0.008
Duration of stay	4.628
Incubation time	0.166
Patient intake	0.218
CRP	0.021

Table II: Qualitative prognostic variables in our study

Qualitative Variables	Death		p (Chi 2)
	Number	Percentage	
Sex	Male	9 53 %	0.579
	Female	2 66 %	
Number of wounds	Unique	7 50 %	0.547
	Multiple	2 66.7 %	
Wound depth	Superficial	4 100 %	0.05
	Deep	5 38,5 %	
Wound size	< 3 cm	8 53.3 %	0.959
	> 3 cm	1 50 %	
Signs of infection		6 60 %	0.419
Paroxysms		9 50 %	0.189
Fever		8 53.3 %	0.604
Anemia		3 60 %	0.604
Leukocytosis		7 70 %	0.185
Renal failure		5 100 %	0.03
Neuro-vegetative disorders		6 100 %	0.012
UTI		1 33.3 %	0.421
Bacteremia		5 100 %	0.03
Pneumopathy		7 50 %	0.426
Tracheotomy		3 50 %	0.298
Antibiotic	Penicillin G	2 40 %	0.876
	Metronidazole	9 60 %	

DISCUSSION

Tetanus is a severe acute toxigenic infection caused by the neurotropic exotoxin of *Clostridium tetanii*, an ubiquitous anaerobic bacillus, spores of which can be found in the soil. This disease is perfectly preventable through vaccination. Tetanus, almost non-existent in developed nations, remains a serious health issue in developing countries, affecting 0.7 to 1 million people / year worldwide, with a mortality rate ranging from 11 to 50% in adults. [1]

In 2013, 12 cases were reported in Morocco, one in Tunisia, 264 in Egypt, 20 in Romania, 9 in France and Spain, 36 in the United States and 2 in Canada. In France, between 2009 and 2014, 8 to 14 cases of tetanus were reported per year, which corresponds to an incidence of 0.06 to 0.22 case per million inhabitants. [2] This incidence can be explained by the generalization of the vaccination and its ten-year boosters all throughout life. In Morocco, the number of annual cases of tetanus varies between 12 and 40 per year. In our study, we noted 20 cases over 5 years, which represents almost 4 cases per year in our hospital.

Clostridium tetani, the cause of tetanus, is a gram-positive, obligate anaerobe, mobile bacillus. It can be found as vegetative form and/or spore form. Spores, highly resistant to chemical and physical agents, can survive in the soil for several years

away from the sun [3-5]. The germination of spores leads to the toxic vegetative form of the tetanus bacillus. Tetanus toxins:

Tetanolysin and tetanospasmin are synthesized at the end of the active growth of the bacillus and released during its autolysis [5-7]. From the entry site, the tetanus toxin reaches the various neurons through hematogenous, neural and lymphatic pathways. It penetrates the nervous system through the neuromuscular junctions of the motor neurons nearest to the entry site. The Toxins get processed through endocytosis, internalized and transported using an axonalretrograde route which makes it inaccessible to antitoxins. [5; 6] It targets a specific synaptic vesicle membrane protein called synaptobrevin. [8] Tetanospasmin hinders the release of inhibitory neurotransmitters Glycine and Gamma-Aminobutyric Acid (GABA) which results in a simultaneous contraction of agonist and antagonist muscles at the origin of reflex spasms. [4; 9]

In the autonomic nervous system, the blocking of inhibitory synapses and the increased secretion of catecholamines cause a sympathetic hyperactivity. There is also a parasympathetic hyperactivity due to the increased synthesis, storage and release of acetylcholine, combined with a cholinergic action specific to the toxin. The effect of the tetanus toxin depletes spontaneously after around 15 days. [4; 9] The age of the patients (50 on average) in our sample represents one of the peculiarities of our

study. In developed countries, at-risk groups are older. [10] In Poland, 65% of patients with tetanus were older than 60 years [11], and in France, 86% were older than 70 years. [12] This is probably due to the generalization of anti-tetanus vaccination, and ten-year boosters in most of the developed nations.

As in third world countries, men in our study are 5.6 times more affected than women. There is a clear male predominance in Benin (Sex ratio at 3.6) [13] and in Brazil (Gender ratio at 5) [14]. This could be explained by the risky manual labor of men in underdeveloped countries. This contradicts data from most developed nations, where women are more affected than men. In France and Poland for example, they represent respectively 75% and 64% of people affected with tetanus [11-12]. Mandatory vaccination during military service could explain these results. [15; 16]

As a matter of fact, even though the anti-tetanus vaccination coverage does not exceed one-third in some sub-Saharan countries [17], against a coverage between 60 and 100% in Europe (97% in France), the contamination by tetanus is more often due to lack of booster vaccination than to the lack of immunization coverage in children. [18]

The diagnosis of tetanus is clinical and should be considered following the early initial symptoms, especially if those symptoms occur following a wound, or in a person with defective vaccine status. The main way of contamination in third-world countries defers a lot from that in industrialized nations: in the latter, wounds are related to domestic activities or gardening, while in the former, Africa for example, wounds result from disregard or lack of knowledge as to the basic rules of asepsis, especially from neglected feet injuries or from some traditional practices (piercings, scarification or tattoos) [4; 19]. The entry site can also be gynecological in sub-Saharan Africa (deliveries and abortions) [20]. Finally, intravenous

drug users represent a risk group that should not be neglected, as it accounts for up to 15% of tetanus patients in the United States. [18]

Incubation period of tetanus varies from less than 24 hours up to 3 weeks [11; 12]. The short length of this period is a determining factor in the prognosis. [4; 5] In our series, the incubation period varied between 3 and 17 days, with an average of 8 days. We did not establish a relationship between incubation time and mortality ($p = 0.16$).

The first symptom is most often trismus, defined by a permanent, painful and bilateral contracture of masseter, rendering opening the mouth impossible. [21] We have witnessed this sign in all our patients. Some observations have described different modes of revelation: facial muscles contraction (sardonic facies), dysphagia, and even abdominal defense [5]. The contractures can be generalized from the outset or initially located. In some cases, there is no secondary generalization [22].

The length of the invasion phase, which averages 48 hours, could have a prognostic value [4; 19]. This was not brought to light in our study. The invasion phase is followed by the occurrence of generalized contractures and reflex spasms (or paroxysms). Reflex spasms are paroxysmal reinforcements of the muscular tone, occurring either spontaneously or after even the smallest sensory stimuli. These spasms can be tonic or, in the most severe forms, tonic-clonic. [19; 21] In our series, we noted a single case of tetanus without generalized contracture, with only a local trismus and favorable evolution in a few days. Other localized forms affecting the mouth, face, limbs and abdomen were described in the literature. [23-25]

The severity of tetanus can be assessed by the Dakar score. It makes it possible to classify tetanus in 7 classes ranging from 0 to 6 based on the presence or absence of 6 clinical elements [**Table III**].

Table III: Dakar Severity Score

Prognostic factors	1 Point	0 Point
Incubation period	< 7 days	> 7 days or unknown
Period of onset	< 2 days	> 2 days
Entry site	Umbilicus, uterus, burns, complex open fractures, surgical procedure, intramuscular injection.	Other or unknown
Paroxysms	Present	Absent
Rectal Temperature	> 38°4	< 38°4
Cardiac frequency:		
Adult	> 120 / min	< 120 / min
New born	> 150 / min	< 150 / min

This score defines 3 groups:

- Group I: Score 0-1: Mild forms
- Group II: Score 2-3: Moderate forms
- Group III:
 - Score 4: Severe forms
 - Score 5-6: Very severe forms

In our series, at admission, 6 patients presented a mild form of the disease, 11 patients had a moderate form, 2 had a severe form and one patient had a severe form. During their hospitalization, 19 patients progressed to group II and III.

A unilateral trismus can be caused by a peritonsillar phlegmon or a neurological event, both needs to be ruled out through differential diagnosis. Strychnine poisoning associated to generalized contractures can mimic the state phase of severe tetanus. [4; 19]

The treatment of tetanus is both symptomatic and etiologic. Symptomatic treatment should be initiated in the intensive care unit. The strict sensory isolation is no longer mandatory, given the use of sedatives. [26] A central venous catheter is placed to meet the fluid and nutritional needs of the patient during his stay in intensive care. A urinary catheter is often put in place to avoid causing a distention of the bladder. Nutritional intake is prerequisite in tetanus patients, to prevent the occurrence of immune deficiency, which would increase the risk of contracting a nosocomial infection. This intake should range from 2000 to 3000 kcal / day. [9; 27] In curare receiving patients, and due to the digestive tract paralysis, this intake should be exclusively parenteral. [28] Finally, physical therapies, both motor and chest physiotherapy, should be initiated as soon as possible to prevent the development of para-osteo arthropathies that may compromise and even worsen the future functional prognosis. [29]

The disinfection of the entry site, when found, is part of the therapeutic algorithm. Saline solution is used in the process, followed, for soiled wounds (under anesthesia) by deep cleansing using a brush and polyvidone iodine or chlorinexidine. [30]

The use of antibiotics, although very controversial, is still recommended in treating severe forms of tetanus. Specifically that of Penicillin G at a dose of 4 to 10 million units per day, although the use of Metronidazole at 500mg per 5 hours for a period of 7 to 10 days has hugely improved the survival rate (7% versus 24% in the penicillin group). [31-32]

The use of anti-tetanus serum is essential in severe tetanus. A dose of 250 UI was given subcutaneously or intramuscularly. This dose can be increased to 500 IU if the wound is infected or is more than 24 hours old, and in patients weighing more than 80 kg. [15; 16; 33] This serum neutralizes the tetanus toxin in a rapid manner,

which ensures a swift, effective protection against tetanus. The vaccine on the other hand, provides long-term protection (from 1 to 14 days) through an active immunization process. The action of anti-tetanus serum is rapid (Detection of serum peaks 2 to 3 days after injection) and lasts an average of 3 weeks. [17]

Despite a well-conducted treatment, patients with severe tetanus may be at risk of developing fatal complications. Nosocomial infections top the list of complications, especially pulmonary infections [25; 34]. Neuro-vegetative disorders are the second most common complication. [34] This is consistent with the results of our study.

Tetanus mortality rates are variable, but remain globally high. In 2011, mortality rate was at 47.8% in France [12], 35.7% in Poland [35]. A 2006 study conducted in Morocco showed a mortality rate of 63.4% [36]. In our study, the mortality was at 55%. A similar study conducted in our department between 2003 and 2008 showed a mortality rate of 60%. [37]

Death can be attributed directly to tetanus, through the various neuro-vegetative disorders it generates, or indirectly, through following complications. Nosocomial infections, especially respiratory infections, are the most common cause of death in various studies [36]. In our series, 45.5% of deaths were caused by septic shock, followed by neuro-vegetative disorders.

Mortality risk factors differ from one study to another. Advanced age and long hospital stay were associated with a high mortality rate in the Hounkpe study [13]. TheDerbie study presented a significant association between the type of complications and the degree of severity of tetanus, and a high mortality rate [34]. In Chakir's study, the short hospital stay, the short incubation period, and having to resort to respiratory resuscitation, plus a high DAKAR score were all considered mortality risk factors. [36] Our study did not shed a light on any of these factors. This could be due to the small size of our sample, which did not allow a multivariate analysis. The risk factors for mortality in our series were: advanced age, elevated CRP levels, wound depth, renal failure, neuro-vegetative disorders, and sepsis.

The treatment of tetanus is mainly preventive. It is based primarily on identifying the wounds at risk and checking the patient's vaccination status. Tetanus quick test is an immunochromatographic, unitary, simple, rapid and reliable test for the detection of specific tetanus antibodies. It allows the specific targeting of unprotected people requiring serotherapy. It has a high sensitivity and specificity, 83% and 97.5% respectively [38]. The prescription of both anti-tetanus serum and vaccine

to all patients unaware of their vaccination status is common in Morocco where this test is not available. The use of tetanus vaccine should not be mandatory if the last booster dose was received in the past 5 years.

Furthermore, are considered at risk of developing tetanus, wounds left untreated for more than six hours, or if, at some point after the trauma, they showed one or more of the following: puncture-like wound, presence of important devitalized tissue, clinical signs of infection, contamination with soil or dirt that may contain tetanus bacilli, burns, frostbite, and high velocity projectile wounds. [39] In our study, most wounds were unique (82%), not exceeding 3 cm in size (53%), deep (76%), and macroscopically clean (59%), most often located on the lower limbs.

CONCLUSION

Severe tetanus is still a major concern in third world countries mainly due to the youthfulness of the target population and the very high mortality rate reported. The diagnosis is mainly clinical; trismus being the most characteristic symptom. Despite advanced resuscitation measures, respiratory, infectious and cardiovascular complications continue to be responsible of a significant mortality rate. The tetanus sero-vaccination remains the only way to prevent tetanus. It becomes more and more urgent to draw the attention of health authorities to this issue, in order to raise public awareness, and to put more emphasis on regular vaccination campaigns as well as good epidemiological surveillance by the health monitoring program to ensure an efficient preventive control.

Conflict of interest

The authors declare no conflict of interest regarding the redaction of this article.

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