



## Clinical Aspects of Tetanus in Bali, Indonesia

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### Abstract

Tetanus is well known for its significant effects to human body. It may cause neurological deficit, systemic symptoms, and mortality in worse cases. The aim of this study was to describe comprehensive clinical aspects of tetanus in Sanglah Hospital. Tetanus prevalence in Sanglah Hospital, from June 2014 - December 2015, were 29 cases. The majority of age was less than 60 years old, predominantly were male patients. All of tetanus cases were classified as moderate-severe general tetanus. We recommended DAKAR classification in order to determine prognosis of tetanus. Most prevalent symptoms were trismus, rigidity and muscle spasm. All patients were hospitalized in isolation ward. There were tendencies to use more than one kind of antibiotics. Metronidazole and cephalosporin were the most frequently used as they were recommended by other researchers. This research showed critical period of treatment for general tetanus were on 6-7 days of admission. Mortality rate of tetanus cases in Sanglah Hospital were 27.6%. Factors that associated with mortality were incubation periods, aspiration pneumonia, sepsis, high fever and opisthotonus.

**Keywords:** *Tetanus, Prevalence, Symptoms, Treatment, Mortality.*

### Introduction

Tetanus is one of health problems worldwide, particularly in developing countries. This disease can affect all ages with a high percentage of mortality. [1] Currently, tetanus occur in 1,000,000 people per year worldwide. The death rate of about 213,000 – 293,000 per year worldwide. [2-3] Most patients were neonates in tropical developing countries.[4] The mortality rate is approximately 10% in the case of mild to moderate, but increased to 60% in severe cases. [5] In Indonesia, annual incidence is 0.2 per 100,000 population. The disease is 69% over the age of 15 years and the incidence has declined since 1990 as a result of the success of the primary immunization program initiated since 1974 by the Indonesian government. [6] Tetanus is caused by *Clostridium tetani*; is an obligate anaerobic bacterium shaped rod/gram positive rods; organisms has mainly been on the ground. Vegetative *Clostridium tetani*

produces two exotoxin namely: tetanospasmin neurotoxin and hemolytic toxin tetanolysin. Tetanospasmin also called tetanus toxin because this toxin causes symptoms of tetanus. [7-11] Tetanus toxin is very potent; estimated lethal dose of 2.5 ng/kg (1 gram of toxin lethal doses equivalent to 6,000,000 adults weighing 60 kg). So that the amount of toxin is relatively less to stimulate the immune system; toxoid injection is needed to achieve active immunization. [2,11,12]

The diagnosis is purely made by clinical symptoms. There are four types of tetanus: general tetanus, cephalic, neonatal, and localized. Patients who survived from tetanus, generally experienced both physical and physiological sequelae. Factors that predict poor prognosis in Africa were old age, a short incubation period, short onset period, type of generalized and severe, disotonomia,

pneumonia, sepsis, hypoxemia and renal failure. [8,13,14]

Comprehensive study of the clinical aspects of tetanus has never been done in Sanglah Hospital. Based on the description above, we would like to do a good research on the clinical aspects i.e prevalence, symptoms, treatment, including tetanus mortality predictors in Sanglah Hospital in 2014-2015.

## Methods

This study was a retrospective cohort study, history and clinical data documentation and measurements were collected from medical records in Sanglah Hospital. This research was conducted in the Surgery and Neurology ward at Sanglah Hospital. The target population was all patients who were treated due to tetanus. This study was approved by ethics committees of Sanglah Hospital. Data provided in descriptive mean, standard deviation, frequency distribution and percentage. Data analysis in this study was using statistical program for social science program (SPSS) version 20.0 for Macintosh. Significance level was  $p \leq 0.05$  with 95% confidence interval (CI). Cross tabulation was used to assess the association of dichotomous variables by a 2x2 table.

## Results

This research obtained 80 patients and only 29 subjects were qualified, since June 2014 -

December 2015. In Table 1, most subjects consisted of 24 (82.8%) males, age 60 years and below (15 patients; 51.7%). Subjects had an incubation period of more than seven days were 17 people (58.6%), the period of onset of 3 days were 15 people (51.7%), injuries to the extremities (27 patients; 93.1%), the location of trauma was at home (15 patients; 51.7%). Most people who had experienced symptoms of muscle spasm (28; 96.6%), rigidity by 26 (89.7%), trismus in 27 patients (93.1%), opisthotonos and seizures were 19 (65.5%) patients. Most of the study subjects experienced symptoms of trismus moderate total of 18 (62.1%) patients, while 5 (17.2%) and 4 (13.8%) of patients experiencing mild and severe trismus respectively.

A small portion of the study subjects experienced symptoms of rhesus sardonicus (3; 10.3%), labile blood pressure (7; 24.1%), fever (14; 48.3%), secondary infection (5 people ; 17.2%), aspiration pneumonia (6; 20.7%), disotonomia (6; 20.7%), hypoxemia (2; 6.9%) and sepsis (12; 41.4% ), as showed in Table 2. There was no patients who experienced tachycardia and diaphoresis without fever. Most of the subjects never got the tetanus vaccine by 24 (82.8%) of patients, 4 patients (13.8%) with partial vaccination, and 1 (3.4%) patients with complete vaccination history.

**Table 1: Characteristic of study subjects**

| Variable (n=29)        | Mean $\pm$ SD     | Minimum | Maximum |
|------------------------|-------------------|---------|---------|
| Age                    | 57.41 $\pm$ 15.18 | 5       | 80      |
| Length of stay         | 12.59 $\pm$ 7.25  | 3       | 31      |
| DAKAR score            | 2.66 $\pm$ 1.14   | 1       | 4       |
| Phillips score         | 15.97 $\pm$ 2.57  | 8       | 19      |
| Prognostic score       | 2.76 $\pm$ 0.44   | 2       | 3       |
| White Blood Cell (WBC) | 10.75 $\pm$ 4.61  | 3.70    | 26.30   |
| Neutrophils            | 8.43 $\pm$ 4.57   | 2.10    | 25.10   |
| Neutrophils %          | 74.90 $\pm$ 10.93 | 51.30   | 96.50   |
| Lymphocyte             | 1.39 $\pm$ 0.53   | 0.50    | 2.90    |
| Lymphocyte %           | 15.23 $\pm$ 8.09  | 2.30    | 38.30   |

The entire research subjects who were treated in Sanglah Hospital, year 2014-2015, included the classification of generalized tetanus; as many as 23 patients (79.3%) with severe degree, 6 patients (20.7%) with moderate degree, and none was classified as mild tetanus. The research subjects who died of tetanus as many as 8 people (27.6%) during the year 2014 - 2015. The mean age of the study subjects in mortality group was  $56.88 \pm 12.79$  years, while the survived group

$57.62 \pm 16.28$  years. The mean difference was not significant ( $p = 0.909$ ).

Based on Kolmogorov-Smirnov test showed the entire distribution of numerical data was normally distributed, so that we use the average analysis using t-test. The DAKAR score in the mortality group of  $3.38 \pm 0.74$ , while survived group of  $2.38 \pm 1.61$ . The mean difference was significant (0.07;  $p = 0.034$ ). Most of the study subjects had higher

levels of white blood cells (WBC) in 18 patients (62.1%), neutrophils (16; 55.2%) were normal. While there is no research subjects who had higher levels of lymphocytes increases.

Differences between the mean of WBC levels ( $p = 0.450$ ), neutrophils ( $p = 0.551$ ), the levels of lymphocytes ( $p = 0.233$ ), and the

percentage of lymphocytes ( $p = 0.310$ ) were not statistically significant. There were three patients (10.3%) who received cardiovascular drugs during the treatment. (Table 2) The whole patients of this study received antibiotic therapy among them 25 patients (86.2%) had more than one kind, more than two kinds were given in 3 patients (10.3%).

**Table 2: Variable and statistics data**

| Variable              | Category        | Dead (%) | Alive (%) | p-Value | OR/RR (95% CI) |
|-----------------------|-----------------|----------|-----------|---------|----------------|
| Age                   | > 60 year       | 4 (50)   | 10 (47.6) | 0.617   | 1.100          |
|                       | ≤ 60 year       | 4 (50)   | 11 (52.4) |         |                |
| Sex                   | Laki-laki       | 6 (75)   | 18 (85.7) | 0.425   | 0.500          |
|                       | Perempuan       | 2 (25)   | 3 (14.3)  |         |                |
| Incubation            | ≥ 7 days        | 1 (12.5) | 16 (76.2) | 0.003*  | 0.045          |
|                       | < 7 days        | 7 (87.5) | 5 (23.8)  |         |                |
| Onset                 | ≥ 3 days        | 3 (37.5) | 12 (57.1) | 0.298   | 0.450          |
|                       | < 3 days        | 5 (62.5) | 9 (42.9)  |         |                |
| Length of stay        | > 2 weeks       | 2 (25)   | 11 (52.4) | 0.183   | 0.303          |
|                       | ≤ 2 weeks       | 6 (75)   | 10 (47.6) |         |                |
| Trismus               | Mild            | 5 (62.5) | 18 (94.7) | 0.065   | 0.093          |
|                       | Severe          | 3 (37.5) | 1 (5.3)   |         |                |
| Hypoxemia             | Present         | 2 (25)   | 0 (0)     | 0.069   | 4.500          |
|                       | Absent          | 6 (75)   | 21 (100)  |         |                |
| Aspiration Pneumonia  | Present         | 6 (75)   | 0 (0)     | 0.000*  | 11.500         |
|                       | Absent          | 2 (25)   | 21 (100)  |         |                |
| Sepsis                | Present         | 8 (100)  | 4 (19)    | 0.000*  | 0.333          |
|                       | Absent          | 0 (0)    | 17 (81)   |         |                |
| Disotonomia           | Present         | 3 (37.5) | 3 (14.3)  | 0.190   | 3.600          |
|                       | Absent          | 5 (62.5) | 18 (85.7) |         |                |
| Labile Blood Pressure | Present         | 3 (37.5) | 4 (19)    | 0.282   | 2.550          |
|                       | Absent          | 5 (62.5) | 17 (81)   |         |                |
| High fever            | Present         | 7 (87.5) | 7 (33.3)  | 0.013*  | 14.000         |
|                       | Absent          | 1 (12.5) | 14 (66.7) |         |                |
| Tetanus Degree        | Moderate        | 0 (0)    | 6 (28.6)  | 0.114   | 1.533          |
|                       | Severe          | 8 (100)  | 15 (71.4) |         |                |
| Rhesus sardonicus     | Present         | 0 (0)    | 3 (14.3)  | 0.364   | 1.444          |
|                       | Absent          | 8 (100)  | 18 (85.7) |         |                |
| Opistotonus           | Present         | 8 (100)  | 11 (52.4) | 0.018*  | 0.579          |
|                       | Absent          | 0 (0)    | 10 (47.6) |         |                |
| Muscle Spasme         | Present         | 8 (100)  | 20 (95.2) | 0.724   | 0.714          |
|                       | Absent          | 0 (0)    | 1 (4.8)   |         |                |
| Rigidity              | Present         | 8 (100)  | 18 (85.7) | 0.364   | 0.692          |
|                       | Absent          | 0 (0)    | 3 (14.3)  |         |                |
| Seizure               | Present         | 7 (87.5) | 12 (57.1) | 0.135   | 5.250          |
|                       | Absent          | 1 (12.5) | 9 (42.9)  |         |                |
| Secondary Infection   | Present         | 0 (0)    | 5 (23.8)  | 0.171   | 1.500          |
|                       | Absent          | 8 (100)  | 16 (76.2) |         |                |
| Antibiotics > 1       | Present         | 8 (100)  | 17 (81)   | 0.252   | 0.680          |
|                       | Absent          | 0 (0)    | 4 (19)    |         |                |
| Cardio drugs          | Present         | 1 (12.5) | 2 (9.5)   | 0.636   | 1.357          |
|                       | Absent          | 7 (87.5) | 19 (90.5) |         |                |
| Entry wound           | Present         | 8 (100)  | 19 (90.5) | 0.517   | 0.704          |
|                       | Absent          | 0 (0)    | 2 (9.5)   |         |                |
| Wound location        | Ekstremitas     | 7 (87.5) | 20 (95.2) | 0.483   | 0.350          |
|                       | Non ekstremitas | 1 (12.5) | 1 (4.8)   |         |                |
| Place of injury       | House           | 5 (62.5) | 10 (47.6) | 0.383   | 1.833          |
|                       | Non House       | 3 (37.5) | 11 (52.4) |         |                |
| WBC                   | Normal          | 6 (75)   | 12 (57.1) | 0.330   | 2.250          |
|                       | Increase        | 2 (25)   | 9 (42.9)  |         |                |
| Neutrophils           | Normal          | 4 (50)   | 12 (57.1) | 0.526   | 0.750          |
|                       | Increase        | 4 (50)   | 9 (42.9)  |         |                |
| Neutrophils %         | Normal          | 5 (62.5) | 12 (57.1) | 0.568   | 1.250          |
|                       | Increase        | 3 (37.5) | 9 (42.9)  |         |                |

\* = significant ( $p < 0.05$ )

The entire research subjects were treated in isolation rooms. Duration of treatment

mostly two weeks (16; 55.2%). The mean duration of treatment in the mortality group

was  $6.13 \pm 4.70$  days, while the survival group was  $15.05 \pm 6.538$  days. The mean difference was statistically significant (0.30;  $p = 0.002$ ).

Cross tabulation analysis (Chi-square) showed a significant relationship with a weak negative correlation between the incubation period to mortality ( $-0.578$ ;  $p = 0.002$ ). Cross tabulation analysis showed a significant relationship and a strong correlation between aspiration pneumonia ( $0.828$ ;  $p = 0.000$ ), sepsis ( $0.735$ ;  $p = 0.000$ ) for mortality result. There were significant relationship and a weak correlation between the categories of high fever ( $0.484$ ;  $p = 0.013$ ), and opisthotonus ( $0.448$ ;  $p = 0.018$ ) for mortality result.

## Discussion

This study was a first hospital-based study of tetanus cases in Sanglah Hospital, Bali. The strength of this study was using all patients that were documented in June 2014 - December 2015 from Neurology and Surgery departments in Sanglah Hospital. Demographic data and characteristics of study subjects were listed in Table 1. Total patients were 29 people, the mean age of the study subjects was  $57.41 \pm 15.18$  years of relatively young, and the majority (51.7%) subjects aged below 60 years. This was different in Italy and Japan which are largely occupied by elderly patients.[7]

The elderly tend to be exposed to tetanus because someone in this age group are prone to trauma from falls or traffic accidents, and the unavailability of vaccines against tetanus in their young age.[1,7] Youths in Ethiopia tend to suffer from tetanus due to the activeness of the youth at the time of development.[13]

In accordance with the distribution of tetanus cases in Japan [1], and Ethiopia (77.9%)[13], most of tetanus cases in Sanglah Hospital were male (82.8%). It is estimated that it is related to the activity of men is higher than women, causing a tendency of trauma.[13] Old age is known to be associated with patient's mortality in Africa.[8,13,14] However, in this study there was no significant relationship between age categories and sex on mortality of research subjects.

## Incubation Period and Period of Onset with Mortality

The whole subject of this research including generalized tetanus that mostly (41.4%) have an incubation period of less than seven days and most (48.3%) onset period is less than three days. This is similar to Hsu and Groleau (2001) which mentions the generalized tetanus incubation period of about 7-10 days (range 2-30 days) depending on the distance of the wound site with the central nervous system. The incubation period generally ranges from 7-9 days in severe cases, as well as the onset of a period of about 48 hours. [4]

This study showed a significant relationship and a weak correlation between the incubation period to mortality ( $0.045$ ;  $p = 0.002$ ). This shows, the shorter incubation period the higher mortality, in patients with generalized tetanus in Sanglah Hospital. The period of onset and short incubation known to be associated with poor prognosis in patients with tetanus in Africa. [8,13,14]

## Status of Vaccination with Mortality

Unknown vaccination history is important in order to establish the diagnosis and prognosis of tetanus which affect the vast majority (82.8%) of this research. Those never had a tetanus vaccine completely, this situation is similar to the study in Italia.[1,7] Tetanus vaccination is especially important to people who are considered vulnerable namely: work on the construction, farming, agriculture, land, police, firefighters, soldiers, housewives and people aged over 60 years.[1,15,16] Serological data in Italy also concordance with this research that showed most of the population aged over 65 years never had primary vaccination against tetanus.

Therefore, a high incidence of tetanus in the elderly is due to low vaccination coverage, not because of low immunity status. Age 50 years is the age recommended in Italy to check the status of a person's immunity against tetanus. [7] It is estimated that only 28-50% of the population aged 65-70 years were immunized with either. Tetanus vaccination on someone who previously non-immune, provide protective capability of 81-95% after administration of the second dose and 100% after the third dose. [4]

## Location and Wound Site with Mortality

Most (93.1%) of this study subjects suffered injuries in the extremities that lead to tetanus i.e. 79.3% in the lower extremities. Location wound that was dominant in the lower extremities, which were consistent with the study of tetanus in Italy in 2001-2010 which was as much as 62.7% and in Ethiopia, was 50%. [7, 13] Based on the location of trauma, in this study the majority (51.7%) occurred in the household environment. By contrast to studies, in Italy the order of the scene trauma ranging from agriculture land (45.2%), agriculture activity (26.9%), households (15%), traffic accidents (7%) and others (5.9 %).<sup>6</sup> The further analysis shows the location of the wound in the body not related ( $p = 0.483$ ) to subject's mortality.

## Symptoms and Complications of Tetanus with Mortality

Subjects in this study showed typical symptoms correspond to generalized tetanus symptoms. Trismus as an early symptom that can be checked in 75% of patients in Japan. [1] In Ethiopia, trismus was the initial symptom in 57.8% cases and 100% appears on the distribution of whole symptoms. [1] Most of the study subjects experienced symptoms of muscle spasms (96.6%), rigidity (89.7%), trismus (93.1%), opisthotonos and seizures (65, 5%). A total of 62.1% of the study experienced symptoms of moderate trismus. If hypertonicity likely to appear on the middle / central body (face, neck, chest, back and abdomen) than in the extremities, it is more likely patients will suffer from tetanus. [1,8,11,15] Distribution of the most common symptoms are consistent with Amare et al. the three most common symptom trismus (100%), rigidity (92.6) and muscle spasms (91.2%), 5 patient's mental status has not changed in patients with tetanus, therefore muscle spasms coincided with severe pain. [4] While a small portion of the study subjects experienced rhesus sardonicus symptoms as much as 10.3%, 24.1% labile blood pressure, high fever 48.3%, 17.2% secondary infection, disotonomia 20.7%, and 6.9% hypoxemia.

These symptoms are symptoms that can appear on a generalized tetanus mainly in severe degrees. [1] This was contrary with Amare et al. (2012) which was done in Ethiopia, that showed 53.8% of patients experienced tetanus hypoxemia in early

physical exam. [13] There were 20.7% of the subjects suffering from aspiration pneumonia and sepsis 41.4%, both known to be associated strongly with mortality research subjects. Both of these complications are the predictor of poor prognosis in African tetanus cases. As for the difference disotonomia and hypoxemia no effect on mortality in this study subjects. [8,13,14] Other symptoms that affect mortality in this study were high fever and opisthotonus, but the power of relationship was not as strong as aspiration pneumonia and sepsis.

## Classification and Tetanus Degrees with Mortality

Phillips score has been established since 1967, the aim of this score is to help determine the degree of severity that can be compared from one region to another. This score is also considered helpful in recording the progression of tetanus and useful to assess the treatment response. [17] Thwaites et al. (2012) tested Phillips, DAKAR and TSS scores (Tetanus Severity Score) to assess the outcomes of tetanus in Vietnam. His research concluded TSS significantly better to Phillips, however no significant difference with DAKAR score who had the area under the curve (ROC curve) expected at 0.74. Sensitivity of Phillips was 89% but had less specificity (20%). DAKAR score has high specificity (98%) but low sensitivity (13%). [18] Average DAKAR score in this research was  $2.66 \pm 1.14$ ,  $15.97 \pm 2.57$  Phillips score and prognosis score of  $2.76 \pm 0.44$ .

The entire research subjects, who were treated at Sanglah during the years 2014 – 2015, were included in the classification of generalized tetanus; 20.7% were moderate and 79.3% severe degree. This distribution was similar to research Amare et al. (2012) in Ethiopia which was dominated by generalized tetanus (91%), based on it's degree, severe tetanus (72.1%) and moderate degree was 19.1%. [13] The mean differences of DAKAR score, between the group of mortality patients and survived patients, was significant ( $0.07$ ;  $p = 0.034$ ).

## WBC, Neutrophils and Lymphocytes with Tetanus Mortality

Increased level of WBC has been known to be associated with progress of infectious diseases. This research obtains mean WBC level slightly increased ( $10.75 \pm 4.61$ ), normal

neutrophil level ( $8.43 \pm 4.57$ ), the percentage of neutrophils slightly increased ( $74.90 \pm 10.93$ ), level of lymphocytes decreased ( $1.39 \pm 0.53$ ), and the percentage of normal lymphocytes ( $15.23 \pm 8.09$ ). Most of the study subjects had higher level of WBC (18; 62.1%), while neutrophils (16; 55.2%) were normal. This was consistent with several studies that showed leukocytosis especially neutrophils, nevertheless all blood test in patients with not significance mean difference in this study, proved there were not associated with mortality of tetanus.

### **Tetanus Therapy with Mortality**

The mortality rate in patients with tetanus in this study was 27.6%. This was slightly lower than the similar study in Japan, which was 28%. Although, There had been provided intensive care and adequate health facilities, mortality rate in tetanus cases remains high, about 20-30%. [1] There were 10.3% populations of this study, who received cardiovascular drugs, during the treatment. The whole subjects of this study were given antibiotic therapy, 86.2% of the subjects were taken antibiotics with more than one kind, while more than two kinds, given to 10.3% of this study. When sorted by the use of most, there were 25 (86.2%) of people received metronidazole therapy, 24 (82.8%) of ceftriaxone, 2 (6.9%) of ampicillin, and 1 (3.4%) received cefixime, gentamycin, cefoperazone and ceftazidime. Meanwhile, the Japanese Society Guideline of Chemotherapy, Japanese Association Guideline for Infectious Disease-2011 and WHO recommendation, giving Penicillin-G and metronidazole therapy for tetanus. [1, 4].

These drugs are superior because their ability to work on the wound with poor vascularization and absces. [4] Penicillin (ampicillin), cephalosporin's (ceftriaxone, ceftazidime cefoperazone), also said to be quite effective for tetanus cases. [2, 4] This study concluded that there were no significant correlation between cardiovascular drugs administration, single antibiotic, and multiple antibiotics on mortality rate.

The median of treatment duration for tetanus study in Italy, showed a longer time compare to this research, which was 25 days longer. This was because the majority of

elderly patients, that were treated in the isolation room. Duration of treatment for most of the study subjects (55.2%) were treated shorter compare to mean duration of the whole subject ( $12.59 \pm 7.25$  days). The mean duration of treatment in the mortality groups were shorter than the survived groups with difference of 11 days and statistically significance ( $0.30$ ;  $p = 0.002$ ). The new finding was that the mean duration of treatment in mortality patients was  $6.13 \pm 4.70$  days, showed a critical period of generalized tetanus patient was day 6<sup>th</sup> of treatment. Amare et al. showed relatively the same period of mean duration of treatment in patients with tetanus who died during 5.9 days. [13]

Although Indonesia has declared free tetanus mother and newborn since 2016, these findings may be ironic, because cases found in Sanglah Hospital were in adults with an average age of about 57 years. The authors estimated that in the past these patients were not fully vaccinated or not completely. [19]

### **Conclusion**

The prevalence of tetanus at Sanglah Hospital in 1 year were 29 cases. Tetanus cases were dominated with less than 60 years of age and male gender. The whole cases were moderate and severe generalized tetanus. DAKAR score was recommended to determine the prognosis. The most common clinical symptoms were trismus, rigidity and muscle spasms. All tetanus patients were treated in isolation room. There was a tendency to use more than one antibiotic during treatment. This study showed the critical period of generalized tetanus patient treatment was day 6<sup>th</sup> of treatment and the factors that influence the mortality were the incubation period, aspiration pneumonia, sepsis, high fever and opisthotonus.

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### **Conflict of Interests**

The authors declare that there is no conflict of interests regarding the publication of this paper.

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