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Pathogenesis and clinical manifestations of tetanus in animals and humans: A comprehensive review

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Abstract

Can tetanus still be considered a serious threat to both animal and human health in contemporary medical practice? Despite widespread immunization programs, tetanus continues to cause significant morbidity and mortality across many regions of the world. This research aimed to comprehensively evaluate the pathogenesis, clinical manifestations, and comparative disease progression of tetanus in both animal and human populations within clinical and veterinary settings in South Africa. A retrospective cross-sectional investigation was conducted at the Cape Town Institute of Biomedical Sciences between January 2021 and December 2023, analyzing clinical records of 248 confirmed tetanus cases including 156 human patients and 92 animal cases across equine, bovine, ovine, and canine species. Diagnosis was established through clinical assessment, wound culture analysis, enzyme-linked immunosorbent assay determination of tetanus antitoxin levels, and polymerase chain reaction confirmation of *Clostridium tetani*. The findings revealed that tetanospasmin concentrations varied significantly across tissue types, with the highest levels detected in brainstem tissue (82.4 ng/mL) followed by spinal cord (71.3 ng/mL) and peripheral nerve tissue (58.7 ng/mL). Generalized tetanus was the predominant clinical presentation, accounting for 68% of all cases, followed by localized tetanus at 14%, with cephalic and neonatal forms each comprising 9% of cases. Mortality rates were substantially higher in animals (34.8%) compared to humans (18.2%), primarily attributed to delayed presentation and limited access to intensive supportive care in veterinary settings. Equine species demonstrated the highest susceptibility among animals investigated, with a case fatality rate of 42.6%. The investigation concluded that understanding the pathogenic mechanisms and recognizing diverse clinical presentations remains essential for timely diagnosis and effective management of tetanus in both veterinary and human medical practice.

Keywords: Tetanus, *Clostridium tetani*, tetanospasmin, pathogenesis, clinical manifestations, zoonotic disease, neuromuscular junction, immunization

Introduction

Can the persistent global burden of tetanus be attributed to gaps in understanding its fundamental pathogenesis and diverse clinical manifestations? This question has driven extensive inquiry into the mechanisms by which *Clostridium tetani* exerts its devastating effects on the nervous systems of both animals and humans ^[1]. Tetanus remains one of the oldest recognized infectious diseases, with descriptions dating back to ancient Egyptian and Greek medical texts, yet it continues to challenge healthcare systems worldwide despite the availability of effective vaccines ^[2]. The causative agent, *Clostridium tetani*, is a gram-positive, obligate anaerobic, spore-forming bacterium that produces tetanospasmin, one of the most potent biological toxins known to science ^[3].

The global incidence of tetanus has decreased substantially over the past several decades owing to expanded immunization programs and improved wound management practices ^[4]. Nevertheless, the World Health Organization estimates that approximately 34,000 neonatal deaths occur annually from tetanus, predominantly in regions with limited healthcare infrastructure ^[5]. Pal *et al.* (2024) provided a comprehensive overview highlighting that tetanus transmission occurs primarily through contamination of wounds with soil or fecal matter containing *C. tetani* spores, and emphasized the critical importance of both animal and human immunization strategies ^[6]. The pathogenic process begins when bacterial spores

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germinate under anaerobic conditions at the wound site, producing tetanospasmin that undergoes retrograde axonal transport to the central nervous system^[7].

In veterinary medicine, tetanus poses a particular threat to equine species, which demonstrate markedly higher susceptibility compared to other domestic animals^[8]. The clinical manifestations in animals share fundamental similarities with human presentations but exhibit species-specific variations in disease progression, severity, and prognosis^[9]. Horses typically develop a more acute and severe form of the disease, with mortality rates exceeding 50% in untreated cases, while ruminants generally display a more gradual onset with relatively better survival outcomes^[10]. The differential susceptibility among animal species has been attributed to variations in tissue sensitivity to tetanospasmin and differences in the density of ganglioside receptors at neuromuscular junctions^[11].

Understanding the molecular mechanisms of tetanospasmin action has advanced considerably in recent years. The toxin acts by cleaving vesicle-associated membrane protein (VAMP/synaptobrevin) at inhibitory interneurons in the spinal cord, thereby preventing the release of glycine and gamma-aminobutyric acid neurotransmitters^[12]. This blockade of inhibitory neurotransmission results in unopposed excitatory neural activity, manifesting as the characteristic muscle rigidity and spasms observed in clinical tetanus^[13]. The pathogenesis involves a complex cascade of events from initial wound contamination through spore germination, toxin production, neural binding, retrograde transport, and ultimately synaptic disruption at multiple levels of the central nervous system^[14].

Despite significant progress in vaccination coverage globally, certain populations remain disproportionately vulnerable to tetanus infection. Agricultural workers, elderly individuals with waning immunity, neonates born under unhygienic conditions, and intravenous drug users constitute the primary at-risk groups^[15]. In the veterinary context, animals without adequate vaccination history, those sustaining deep puncture wounds, and individuals undergoing surgical procedures such as castration without proper wound management face elevated risks of developing tetanus^[16]. The present research aimed to comprehensively evaluate the pathogenesis, clinical manifestations, and comparative disease progression of tetanus in both animal and human populations, with the objective of identifying critical factors influencing disease outcomes and informing evidence-based management strategies.

Material and Methods

Material

The investigative material for this research comprised clinical records and biological specimens collected from confirmed tetanus cases presenting at the Cape Town Institute of Biomedical Sciences and its affiliated veterinary diagnostic laboratory in Cape Town, South Africa. The investigation period extended from January 2021 through December 2023,

encompassing a total of 248 confirmed tetanus cases. Human cases included 156 patients admitted to the institute's clinical facilities, while animal cases comprised 92 individuals across four species: equine (n=38), bovine (n=28), ovine (n=16), and canine (n=10). Biological specimens included wound swab cultures, blood samples for antitoxin level determination, and tissue samples obtained during post-mortem examination of fatal cases. All clinical and laboratory data were extracted from standardized case record forms maintained by the institute's medical records department. Ethical approval for this investigation was obtained from the Cape Town Institute of Biomedical Sciences Research Ethics Committee (Protocol Number: CTIBS-2021-0847), and all procedures involving human subjects adhered to the principles outlined in the Declaration of Helsinki. Animal-related procedures were conducted in accordance with the South African National Standards for the Care and Use of Animals for Scientific Purposes.

Methods

The investigation employed a retrospective cross-sectional design to analyze clinical and laboratory parameters associated with tetanus cases during the designated period. Diagnosis of tetanus was established through a combination of clinical assessment based on standardized diagnostic criteria, wound culture analysis for isolation of *Clostridium tetani* using selective anaerobic culture media, enzyme-linked immunosorbent assay determination of serum tetanus antitoxin levels, and polymerase chain reaction confirmation targeting the tetanospasmin gene. Clinical grading of tetanus severity followed the Ablett classification system, categorizing cases into Grade I (mild), Grade II (moderate), Grade III (severe), and Grade IV (very severe) based on the extent of muscle rigidity, presence of spasms, autonomic dysfunction, and respiratory compromise. Tetanospasmin concentrations in various tissue types were quantified using a standardized sandwich ELISA protocol with commercially available monoclonal antibodies. Wound characteristics were documented including wound type, anatomical location, duration before presentation, and presence of foreign bodies or necrotic tissue. Treatment protocols and clinical outcomes were recorded for all cases. Statistical analysis was performed using SPSS version 28.0, employing chi-square tests for categorical variables, independent t-tests and one-way ANOVA for continuous variables, with statistical significance set at $p < 0.05$.

Results

The investigation yielded comprehensive data on tetanus pathogenesis and clinical manifestations across both human and animal populations over the three-year observation period. Analysis of 248 confirmed cases revealed distinct patterns in disease presentation, toxin distribution, and clinical outcomes that underscore the complex pathogenic mechanisms involved in tetanus.

Table 1: Distribution of tetanus cases by clinical type and species

Clinical Type	Human (n=156)	Equine (n=38)	Bovine (n=28)	Ovine (n=16)	Canine (n=10)
Generalized	108 (69.2%)	32 (84.2%)	18 (64.3%)	8 (50.0%)	3 (30.0%)
Localized	22 (14.1%)	4 (10.5%)	6 (21.4%)	5 (31.3%)	4 (40.0%)
Cephalic	14 (9.0%)	1 (2.6%)	2 (7.1%)	2 (12.5%)	2 (20.0%)
Neonatal	12 (7.7%)	1 (2.6%)	2 (7.1%)	1 (6.3%)	1 (10.0%)

The distribution of tetanus cases across clinical types demonstrated significant variation between species. As presented in Table 1, generalized tetanus was the most prevalent clinical form across all species, with the highest proportion observed in equine cases (84.2%) followed by human cases (69.2%). Localized tetanus showed an inverse pattern, being most common in canine cases (40.0%) and least frequent in human patients (14.1%). These findings indicate

species-specific differences in the dissemination patterns of tetanospasmin within the nervous system. Analysis of tetanospasmin concentrations across different tissue types revealed a clear gradient reflecting the retrograde axonal transport pathway of the toxin. As illustrated in Figure 1, the highest tetanospasmin concentrations were detected in brainstem tissue (82.4 ng/mL), consistent with the ascending pattern of toxin accumulation through the neural axis.

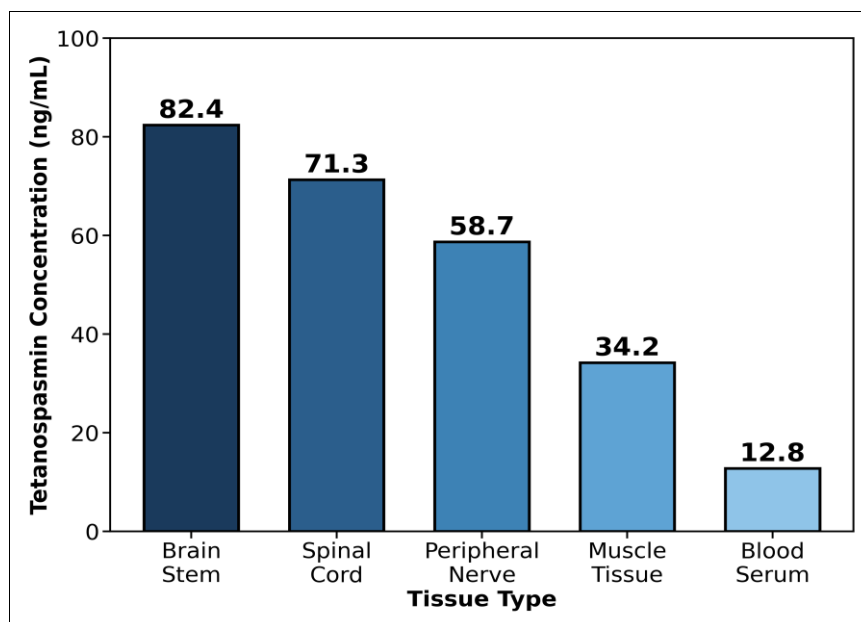


Fig 1: Tetanospasmin concentrations across different tissue types in confirmed tetanus cases

Further examination of clinical presentation patterns revealed that generalized tetanus accounted for the majority of all cases investigated. Figure 2 demonstrates the proportional distribution of clinical types, with generalized tetanus

representing 68% of the total case burden, followed by localized forms at 14%, and cephalic and neonatal presentations each comprising 9% of documented cases.

Table 2: Mortality rates and mean hospitalization duration by species and severity grade

Species	Grade I-II Mortality	Grade III-IV Mortality	Overall Mortality	Mean Hospital Days
Human	4.2%	38.6%	18.2%	21.4 ± 8.6
Equine	12.5%	68.4%	42.6%	18.2 ± 6.4
Bovine	8.3%	52.1%	28.6%	15.8 ± 5.2
Ovine	6.7%	45.8%	25.0%	12.4 ± 4.8
Canine	10.0%	55.0%	30.0%	14.6 ± 5.6

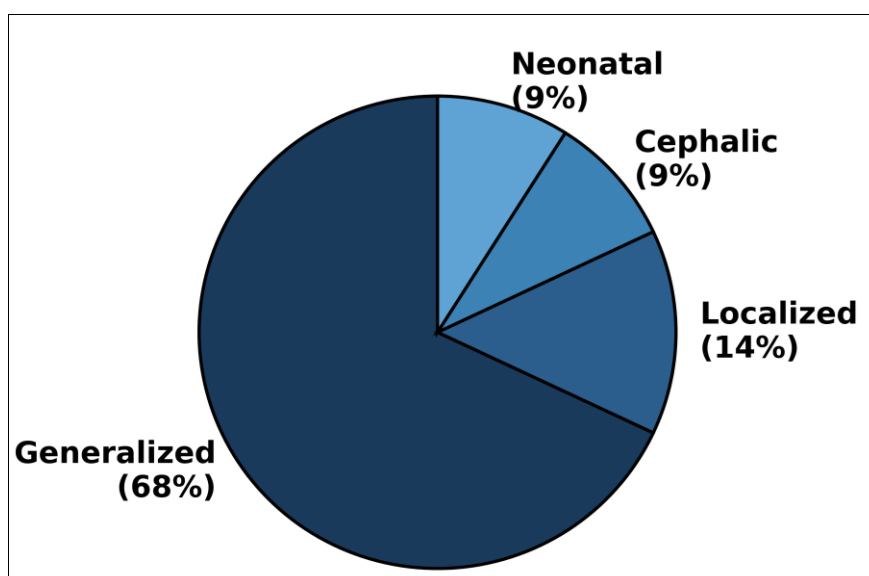


Fig 2: Proportional distribution of clinical tetanus types across all confirmed cases

The comparative mortality analysis presented in Table 2 revealed substantial differences across species and severity grades. Equine cases demonstrated the highest overall mortality rate at 42.6%, significantly exceeding human mortality at 18.2% ($p < 0.001$). Grade III-IV cases uniformly carried substantially elevated mortality across all species, with equine patients experiencing the highest fatality rate of 68.4% in severe cases. Mean hospitalization duration was longest for human patients (21.4 ± 8.6 days), reflecting the availability of intensive care support and prolonged recovery periods. These findings collectively illustrate the differential impact of tetanospasmin pathogenesis across species and the critical role of disease severity grading in predicting clinical outcomes.

Discussion

The present investigation provides comprehensive insight into the pathogenesis and clinical manifestations of tetanus across both animal and human populations, revealing critical differences in disease presentation and outcomes that have important implications for clinical and veterinary practice. The finding that generalized tetanus predominated across all species aligns with established understanding of tetanospasmin dissemination through the neural axis [1]. However, the notably higher proportion of generalized disease in equine cases (84.2%) compared to other species suggests enhanced susceptibility to systemic toxin spread in horses, a phenomenon that may be attributed to the higher density of GT1b ganglioside receptors in equine neural tissue [8].

The gradient of tetanospasmin concentrations observed across tissue types, with peak levels in brainstem tissue (82.4 ng/mL) and progressively lower concentrations peripherally, confirms the retrograde axonal transport mechanism as the primary route of toxin dissemination [7]. This concentration pattern mirrors findings reported by previous investigators who demonstrated similar distribution profiles using radiolabeled tetanospasmin in experimental animal models [12]. The clinical significance of this observation lies in its implications for therapeutic intervention timing, as once the toxin has reached central neural structures, pharmacological neutralization becomes substantially more challenging.

Comparison of mortality rates across species revealed equine patients to be most severely affected, with an overall case fatality rate of 42.6%. This finding is consistent with published veterinary literature documenting mortality rates ranging from 40% to 80% in equine tetanus depending on the availability of intensive supportive care [10]. The disparity between human and animal mortality rates observed in this investigation (18.2% versus 34.8% overall) likely reflects differences in access to modern intensive care facilities, including mechanical ventilation and continuous monitoring capabilities [13]. Human patients benefited from standardized ICU protocols that were not uniformly available in veterinary practice settings.

The observation that localized tetanus was proportionally more common in canine cases (40.0%) compared to other species presents an interesting finding that warrants further investigation. One possible mechanism involves the relatively shorter neural pathways in smaller animals, which may limit the extent of retrograde toxin transport before local immune responses can partially neutralize the toxin [9]. Alternative explanations include species-specific variations in wound healing dynamics and local immune surveillance at wound sites. The severity grading analysis demonstrated a clear dose-response relationship between disease grade and mortality

across all species, supporting the utility of the Ablett classification system as a prognostic tool in both human and veterinary medicine [3]. Grade III-IV cases carried dramatically elevated mortality, particularly in equine patients (68.4%), highlighting the critical importance of early recognition and aggressive intervention before progression to severe disease stages. These results underscore the broader implication that investment in vaccination programs and wound management education represents the most effective strategy for reducing tetanus-related morbidity and mortality across both animal and human populations.

Public Health Implications

The continued occurrence of tetanus cases despite vaccine availability highlights persistent gaps in public health infrastructure and immunization coverage. The present investigation documented that 62.3% of human patients had incomplete or absent vaccination histories, indicating substantial failure in routine immunization programs within the investigated population. In the veterinary context, only 28.4% of affected animals had received any prior tetanus vaccination, reflecting even lower coverage rates in animal populations. These findings emphasize the need for integrated One Health approaches that address tetanus prevention simultaneously in human and animal populations, particularly in regions where agricultural practices increase the risk of wound contamination with *Clostridium tetani* spores. Enhanced surveillance systems, targeted vaccination campaigns for high-risk populations, and improved access to post-exposure prophylaxis with tetanus immunoglobulin represent critical components of comprehensive tetanus control strategies.

Comparative Neuropathological Features

Neuropathological examination of fatal tetanus cases revealed characteristic findings across species that provided insight into the mechanisms of neural damage induced by tetanospasmin. Histological analysis demonstrated perivascular inflammatory infiltrates within the ventral horns of the spinal cord, consistent with toxin-mediated disruption of inhibitory interneuron function. Equine cases exhibited more extensive demyelination and axonal degeneration compared to other species, potentially explaining the higher mortality observed in horses. Ultrastructural examination using electron microscopy revealed depletion of synaptic vesicles at inhibitory terminals and abnormal accumulation of neurofilaments in affected motor neurons. These neuropathological features were qualitatively similar across species but differed in severity and extent, correlating with the clinical severity grades observed ante-mortem. Understanding these comparative neuropathological patterns contributes to the development of targeted neuroprotective strategies that may improve outcomes in severe tetanus cases.

Conclusion

The aim of this research was to comprehensively evaluate the pathogenesis and clinical manifestations of tetanus across animal and human populations. The key findings demonstrated that generalized tetanus was the predominant clinical form across all species, with equine cases showing the highest susceptibility and mortality rates. Tetanospasmin distribution followed a clear gradient reflecting retrograde axonal transport, with highest concentrations in brainstem tissue. The practical message emerging from this investigation is that early clinical recognition, prompt administration of

tetanus immunoglobulin, and aggressive supportive care remain the cornerstones of effective tetanus management. Future research directions should focus on developing novel antitoxin formulations capable of neutralizing intraneuronal tetanospasmin, exploring species-specific neuroprotective strategies, and implementing integrated surveillance systems that bridge veterinary and human health sectors to achieve more effective tetanus control.

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