

# Review of treatment of generalised tetanus in dogs

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## ABSTRACT

This review paper investigates the published evidence for various therapeutic strategies commonly used in the management of generalised tetanus in dogs and cats. The level of the evidence for the efficacy of tetanus antitoxin administration, antimicrobial therapy, wound management and immunotherapy in companion animals was low, review articles citing case reports and small case series, rather than case-control, cohort studies or clinical trials. Untested extrapolation from published data on the treatment of people with tetanus frequently directs recommendations made for the management of tetanus in dogs and cats. There is a need for further studies and evidence-based guidelines for treatment of this condition in dogs and cats. Until then, clinical judgement is required by the veterinarian to determine appropriate treatment. Supportive care remains the mainstay of treatment. *Aust Vet Pract* 2014;44(1):574-578

## INTRODUCTION

Generalised tetanus is a rare but life-threatening neurologic disorder characterised by spastic paralysis, caused by tetanospasmin, a potent neurotoxin produced by the vegetative form of *Clostridium tetani*.<sup>1,2</sup> The organism is a motile, gram-positive, non-encapsulated, anaerobic, slender endospore-forming bacillus.<sup>2,3</sup> Spores are found ubiquitously in soil, faeces, dust and in the gastrointestinal tract of numerous animal species world-wide.<sup>3</sup>

The diagnosis of generalised tetanus is based on characteristic clinical signs,<sup>4</sup> including marked muscle rigidity, particularly of the extensor muscle groups.<sup>5</sup> Initial clinical signs can relate to cranial nerve involvement and include risus sardonicus, trismus, ocular abnormalities (such as third-eyelid protrusion or enophthalmos), erect ear carriage and altered facial expression (Figures 1 and 2).<sup>1,6,7</sup> Other clinical signs include torticollis, urethral and anal sphincter hypertonicity, dyspnoea, coughing, dysphagia, ptyalism, generalised facial swelling, regurgitation, vomiting, trembling, ataxia, spastic tetraplegia, hyperaesthesia, anorexia and lethargy.<sup>1,6-10</sup>

Death can occur from respiratory compromise secondary to rigidity of external respiratory musculature, laryngospasm, increased airway secretions or central respiratory arrest.<sup>2</sup> Subjects are susceptible to complications from prolonged recumbency and paralysis, including urinary and respiratory tract infections, dehydration, malnutrition and decubital ulcers.<sup>2,5</sup> Dogs may be euthanased due to perceived poor prognosis and the expense of prolonged hospitalisation.<sup>7,11</sup>

Therapeutic goals include neutralising unbound toxin, inhibiting the growth of *C. tetani* and further toxin elaboration with antimicrobials, and providing supportive care until the effects of the toxin have dissipated. This review discusses the



**Figure 1.** A 10-week-old female entire mixed-breed puppy with generalised tetanus. Note generalised extensor muscle rigidity, risus sardonicus, enophthalmos and erect pinnae.



**Figure 2.** The same puppy on day 10 following treatment with tetanus anti-toxin, antimicrobials and supportive care. She is attempting to stand, using her chin for additional support.

pharmacotherapy of tetanus and offers a critical insight into the justification for each therapeutic modality.

## ANTITOXIN

Two types of immunoglobulin preparations are available for the treatment of tetanus in Australia. Tetanus antitoxin (TAT) is a purified high titre antiserum derived from horses repeatedly immunized with *C. tetani*, and tetanus immunoglobulin-VF is derived from human plasma. The efficacy of immunoglobulin preparations for the prevention of tetanus in people was first determined over one hundred years ago (and during World War I) yet its efficacy in companion animals is not documented in the literature. It is difficult to assess retrospectively in the clinical setting as antibiotics were administered concurrently in all reported cases where antitoxin was used.<sup>1, 6-9, 11-27</sup>

Tetanus antitoxin is theoretically indicated to neutralise unbound toxin, however tetanus toxin travels within axons and is not accessible to TAT.<sup>5</sup> Furthermore, the large immunoglobulin molecules in TAT cannot readily cross the blood-brain barrier to neutralise the unbound toxin already in the central nervous system, prompting the hypotheses that intrathecal TAT would be more efficacious than antitoxin administered intramuscularly or intravenously. In one study, people treated with a combination of intrathecal and intramuscular antitoxin had reduced muscle spasms, a shorter hospital stay and shorter duration of respiratory assistance than those receiving antitoxin via the intramuscular route exclusively, although there was no difference in mortality or complications.<sup>28</sup> There is however, conflicting evidence about the benefits of intrathecal TAT compared with other routes of administration for people with tetanus. Some clinical trials in people have reported that mortality rate and duration of hospital stay were not significantly different between groups receiving intrathecal therapy compared with intramuscular therapy (IMS)<sup>29, 30</sup> or that intrathecal serotherapy results in higher mortality than IMS,<sup>31</sup> whereas more recent meta-analysis (942 people in 12 clinical trials) concluded that intrathecal administration of equine anti-tetanus serum or human tetanus immunoglobulin is more beneficial than intramuscular administration in the treatment of tetanus.<sup>30</sup> In dogs with mild to moderate tetanus, cisternal intrathecal administration of as low as 1% of the recommended intravenous TAT dose reduced morbidity and mortality, compared with similarly affected dogs given intravenous or lumbar intrathecal injections.<sup>32</sup>

It is possible that prevention of elaboration of further toxin via antimicrobial administration that targets vegetative *C. tetani* plays a more critical role in these subjects. In one case series of 20 dogs, there was no significant difference in survival, or severity or duration of clinical signs in dogs treated with TAT and those that were not.<sup>7</sup> In another case series of 38 dogs, no relationship between timing of administration of TAT, clinical course and outcome was identified.<sup>1</sup>

Minimum dose recommendations for TAT vary from 100-10,000 units /kg SC,<sup>6</sup> with doses of 20,000 units /kg reported.<sup>5,33</sup> Repeat administration (daily,<sup>34</sup> or in one case on days 7 and 9<sup>24</sup>) is mentioned in some reports. Since therapeutic blood concentrations of TAT persist for 14 days, repeat administration is likely unnecessary.

Administration of a test dose of TAT subcutaneously to detect local hypersensitivity reactions is widely practiced,<sup>1,6,7,11-13,19,20,25</sup> but one retrospective case series 38 dogs found that this did not predict TAT hypersensitivity. Reactions were noted in some dogs with a negative skin test result and were not observed in dogs with a positive skin test result which were subsequently treated with TAT.<sup>1</sup> There is no evidence supporting local injection of TAT around and proximal to the wound site for generalised tetanus in dogs and it is not practical when the site of infection is unknown.

## ANTIMICROBIAL THERAPY

The goal of antimicrobial therapy is to eliminate vegetative *C. tetani* organisms and reduce the amount of antitoxin required to treat experimentally-induced tetanus in dogs.<sup>2</sup> Antimicrobial therapy has been shown to reduce mortality and the need for muscle relaxants in people.<sup>35</sup> A case series of 38 dogs found no association between antimicrobial administration and progression of clinical signs or 28-day survival rate.<sup>1</sup> Reduced mortality in people may be due to protection against nosocomial infections which are a common complication of generalised tetanus.<sup>36</sup>

Current antimicrobial recommendations in dogs include penicillin G (20-100000 units/kg IV,IM or SC twice to four times daily); amoxicillin-clavulanate (12mg/kg PO or SC twice daily); metronidazole (10mg/kg PO or IV twice to three times daily); clindamycin (3-10mg/kg IV, IM or PO twice to three times daily) and tetracycline (22mg/kg PO, IV three times daily).<sup>2,5</sup> An ideal antimicrobial agent should demonstrate activity against all strains of *C. tetani*, ability to penetrate poorly perfused and necrotic tissue, ability to be administered parenterally in generalised cases and be devoid of toxicity at therapeutic doses.<sup>37</sup> Historically, penicillin G was the drug of choice because of its excellent anaerobic activity. However, penicillin, like tetanus toxin, is a GABA antagonist and may theoretically worsen hypertonic signs, reduce the efficacy of benzodiazepines and increase the risk of convulsions.<sup>22,38</sup> The extent to which penicillin may access GABA receptors in the absence of disruption to the blood brain barrier is however, unknown. Furthermore, inadequate tissue perfusion at the wound site may reduce delivery of penicillin to the site of local infection.<sup>39</sup> Penicillin derivatives such as ampicillin are not consistently effective against *C. tetani*. In one dog,<sup>8</sup> clinical improvement was reported within hours of changing antimicrobials from sodium ampicillin to penicillin G procaine, though this may have been a coincidental association. Ongoing therapy with high doses of penicillin may predispose subjects to colonisation with resistant organisms, making them susceptible to nosocomial infection.<sup>38</sup>

Metronidazole is the drug of choice for treatment of tetanus in people as it is bactericidal against anaerobes, rapidly achieves therapeutic concentrations in almost all body fluids and tissue, including abscess cavities, and its in vivo activity is not affected by local pH or inactivating enzymes.<sup>39</sup> To the best of our knowledge there are no case reports of metronidazole toxicity in treated dogs with generalised tetanus. The risk of metronidazole toxicity is low at the recommended dose rate of 10mg/kg PO twice daily. Adverse effects of metronidazole in the dog include vomiting, hepatotoxicity and neurologic signs including head tilt, upper motor neurone tetraparesis, ataxia, seizures, nystagmus,

torticollis, opisthotonus, tremors and rigidity,<sup>17</sup> some of which overlap with signs of generalised tetanus. However, neurologic toxicity from metronidazole is only reported in dogs receiving over 60 mg/kg PO daily for 3-14 days.<sup>17</sup> This is over six times the dose recommended for treatment of tetanus.<sup>2</sup> Treatment of metronidazole toxicity involves withdrawal of the drug and administration of diazepam, which may competitively reverse the binding of metronidazole to benzodiazepine sites on the GABA receptor.<sup>17</sup> This hypothesis is unproven, but if it is true, then the fact that the majority of dogs with generalised tetanus are treated concurrently with diazepam may in fact protect against potential metronidazole toxicity in these cases. Even so, the use of high doses of metronidazole in generalised tetanus should be avoided as toxicity may lead to permanent, subclinical damage to neurons and white matter tracts.<sup>17</sup>

## WOUND DEBRIDEMENT

The rationale for surgical wound debridement is based on the assumption that production of the tetanospasmin is a continuous process which can be prevented only by removal or destruction of bacilli.<sup>39</sup> However, one case series of 38 dogs found no significant association between earlier wound management and progression of clinical signs or 28 day mortality rate.<sup>1</sup> On the one hand, removal of devitalised tissue and foreign material coupled with drainage may minimise and inhibit obligate anaerobes in the microenvironment. Flushing the wound with hydrogen peroxide transiently increases oxygen tension in the tissues, which may further inhibit anaerobes,<sup>2</sup> but associated tissue injury may prolong the healing process<sup>10</sup> and this procedure cannot be recommended. In addition, a rare but serious potential complication is the formation of oxygen emboli.<sup>5</sup>

## MUSCLE RELAXANTS

One of the most important aspects of treatment is the administration of agents to control muscle spasms and convulsions associated with tetanus without interfering with voluntary motor or respiratory function.<sup>30</sup> Benzodiazepines, including diazepam, are GABA agonists. Diazepam is favoured because it is a combined anticonvulsant, muscle relaxant, sedative and anxiolytic, but causes less respiratory depression than barbiturates.<sup>30</sup> While diazepam provides rapid relief when administered intravenously, it is relatively short-acting with a half-life of 3.2 hours.<sup>40</sup> According to a case report in a dog, repeat dosing is required at decreasing intervals as the subject develops tolerance to the drug.<sup>41</sup> Methocarbamol may be useful in the later stages of the disease when spasms are reduced in severity,<sup>41</sup> but is also relatively short acting with a half-life of 2.15 hours.<sup>38</sup> In one case series, no dog received methocarbamol for more than a single day before being switched to a different drug.<sup>1</sup>

Autonomic nervous system dysfunction (AD) is rarely reported in animals, but this is likely to reflect inadequate monitoring or recognition of the signs, which include ptialism, tachycardia, tachypnoea and hypertension.<sup>5,22</sup> Autonomic dysfunction is present in up to 30% of people with tetanus and is a predictor of poor outcome, with tachyarrhythmias commonly implicated in deaths.<sup>31</sup> Although AD was more commonly associated with severe tetanus, 40% of people with AD had mild to moderate

tetanus. Autonomic dysfunction has been reported in at least two dogs in an intensive care setting,<sup>11</sup> and may have been present in 7/8 dogs that died or were euthanased in another case series, as these animals had heart rate and or blood pressure abnormalities.<sup>1</sup> Veterinarians should be aware of the possibility of AD in dogs with generalised tetanus and monitor the animals' blood pressure, heart rate, and respiratory rate frequently for evidence of AD.

Magnesium sulphate (MgSO<sub>4</sub>) has been used recently as an adjunct therapy in the management of muscle spasms and AD in people.<sup>42</sup> Magnesium is a non-specific calcium channel blocker that causes muscle relaxation by acting to decrease calcium entry into presynaptic cells at the neuromuscular junction, thereby decreasing acetylcholine (ACh) release, as well as decreasing postsynaptic motor endplate sensitivity to ACh.<sup>42</sup> In addition, MgSO<sub>4</sub> is believed to control AD by decreasing catecholamine release from adrenal glands and peripheral adrenergic nerve terminals while reducing sensitivity of receptors to catecholamines.<sup>42</sup> It may alleviate AD-mediated hypertension by decreasing smooth muscle intracellular calcium, leading to vasodilation.<sup>42</sup> Supraphysiologic magnesium administration has a narrow therapeutic window and treatment may lead to overdose, with signs of overdose ranging from lethargy, nausea, vomiting and mild hypocalcaemia to CNS depression and conduction abnormalities, clinically significant hypocalcaemia, respiratory depression, flaccid paralysis, bradycardia, hypotension and cardiac arrest.<sup>42,43</sup> Animals receiving MgSO<sub>4</sub> therefore require continuous monitoring of the patella reflex for hyporeflexia, as well as serial evaluations of magnesium and calcium, electrocardiography, pulse oximetry and blood pressure.<sup>42</sup> Clinical trials to date provide only weak support for the role of MgSO<sub>4</sub> as an adjunctive antispasmodic agent in people.<sup>10,44</sup> There is only one published case report documenting its use in a dog with generalised tetanus.<sup>42</sup> The dog survived, but assessment of efficacy was impossible since MgSO<sub>4</sub> infusion was commenced on day 7 of treatment. This report only provides circumstantial evidence that the use of MgSO<sub>4</sub> contributed to the successful outcome in this case.

## IMMUNOLOGIC TREATMENT

Clinical disease in dogs and people may not result in protective immunity after infection because the concentration of tetanus toxin required to induce clinical disease is so low.<sup>3,38,44</sup> Recurrent tetanus has been reported in people,<sup>39,45</sup> but to date, not in dogs. In people, tetanus anti-toxoid antibodies of 0.01IU/mL are believed to be protective, based on a guinea pig model.<sup>46</sup> Several cases have however, been reported with measurable antibody concentrations greater than this.<sup>40,45,47,48</sup> Interestingly, in the original study in guinea pigs, 13% of animals developed non-fatal tetanus despite titres considered to be protective.<sup>46</sup> This may be due to antigenic variability between tetanus toxin and tetanus toxoid.<sup>40</sup> Alternatively, the dose of toxin may have exceeded the maximum protective capacity of antibodies.<sup>40</sup>

Active immunoprophylaxis with tetanus toxoid is currently limited to the most susceptible species (horses and people).<sup>2</sup> Due to the relative resistance of dogs and cats to the tetanus toxin, there is little demand in these species, although a vaccine is approved for use in dogs (Equivac T, Zoetis, Australia). The World Small Animal Veterinary Association's current Guidelines for the Vaccination

of Dogs and Cats, compiled by its Vaccination Guidelines Group, provides no discussion of the use of tetanus toxoid in these species and does not list tetanus toxoid as a core vaccine.<sup>49</sup> Whilst an argument could be made for veterinarians to administer TAT to all dogs suffering from contaminated penetrating wounds, the benefits must be weighed against the risk of anaphylaxis and serum sickness (S Mitchell, personal communication, 2011). Given that generalised tetanus is a rare condition in dogs, there is not enough data at this time to justify prophylactic administration of TAT in dogs suffering penetrating wounds.

## CONCLUSION

This review confirms a paucity of evidence on the benefits and harms of major therapeutic interventions used for treating generalised tetanus in dogs, including TAT, antimicrobial therapy, wound management, muscle relaxants and immunologic treatment. There is a need for further studies and evidence-based guidelines for treatment of this condition in dogs and cats. Until then, clinical judgement is required by the veterinarian to determine appropriate treatment. Supportive care remains the mainstay of treatment.

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