

Standard Article

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Clinical Implications and Hospital Outcome of Immune-Mediated Myositis in Horses

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Background: Immune-mediated myositis (IMM) is a cause of rhabdomyolysis, stiffness, and muscle atrophy predominantly affecting Quarter horses. Limited information is available with regard to outcome, prognostic indicators, and associations with concurrent diseases.

Hypothesis/Objectives: To report outcomes and associations between outcome and clinical and laboratory parameters, and presence of concurrent illness.

Animals: Sixty-eight horses; 52 Quarter horses and related breeds and 16 other breeds.

Methods: Retrospective cohort study (1991–2014). Medical records of horses with histological diagnosis of IMM were reviewed. Data recovery included signalment, laboratory variables, therapy, and outcome. Logistic regression was used to quantify the association between potential prognostic factors and survival to discharge.

Results: Quarter horses were younger (mean < 4 years, range 3 months–21 years) than other breeds (mean < 10 years, range 1–23 years). Pathogens causing concurrent or recent infection included *S. equi equi*, *S. equi zooepidemicus*, *C. pseudotuberculosis*, *Anaplasma phagocytophilum*, herpes virus-1, and influenza. The most common clinical signs consisted of rapidly progressive diffuse symmetrical muscle atrophy (80%), stiff gait (74%), and fever (44%). All horses that received medical therapy immediately upon admission survived to discharge (survival proportion = 87%). Leucocytosis was a common finding (60%). Horses with concurrent fever and other illness had a poor prognosis for hospital discharge.

Conclusions and Clinical Importance: Horses with IMM can have a favorable outcome. Horses with concurrent fever and another illness had decreased probability of survival to discharge.

Key words: Equine; Inflammation; Lymphocytes; Myonecrosis.

Immune-mediated myositis (IMM) occurs in humans, dogs, and horses.^{1–8} Immune-mediated myositis has been predominantly described in Quarter horse and related breeds and is characterized by rapid and diffuse symmetrical muscle atrophy predominantly of gluteal and epaxial muscles, lethargy, and stiffness.⁶ The primary laboratory findings include increase in creatine kinase and aspartate aminotransferase activity on a serum biochemistry panel.⁶ The main histological feature of skeletal muscle biopsies is mononuclear cell infiltration of predominantly CD4+ T-lymphocytes and myonecrosis.^{6,9} Immune-mediated myositis belongs to a group of inflammatory myopathies.¹ Myopathies can be classified as noninflammatory and inflammatory

Abbreviations:

AST	aspartate aminotransferase activity
CI	confidence interval
CK	creatinase activity
EMG	electromyography
IMM	immune-mediated myositis
NDL	Neuromuscular Disease Laboratory
SUN	serum urea nitrogen
UC	University of California at Davis
VMTH	Veterinary Medical Teaching Hospital

myopathies. Noninflammatory myopathies are a heterogeneous group of muscle diseases that lack inflammatory cell infiltration as the predominant finding and might present with or without myonecrosis when examined histologically.^{10,11} Inflammatory myopathies are characterized by the presence of inflammatory cell infiltration as the predominant histological finding and myonecrosis and further classified on the basis of distinct clinicopathological features in humans and dogs.^{1,5,12} Inflammatory myopathies can result from infectious and noninfectious causes.¹ Examples of infectious causes in dogs and horses include *Acinetobacter calcoaceticus*, *Clostridium* spp., *Corynebacterium pseudotuberculosis*, *Salmonella infantum*, *Streptococcus equi* subsp. *equi*, *Sarcocystis* spp., *Toxoplasma gondii*, and *Neospora caninum*.^{3,13–19} Noninfectious inflammatory myopathies causes include immune-mediated (dogs, horses) and para- or preneoplastic syndromes (dogs).^{3,6,20}

Noninfectious inflammatory myopathies are the largest group of potentially treatable myopathies in humans and are classified based on clinicopathological features into dermatomyositis, polymyositis, necrotizing autoimmune myositis, inclusion body myositis, and

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The study was performed at the University of California at Davis.

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overlap myositis.¹ Inflammatory myopathies in dogs include muscle masticatory myositis, extraocular myositis, dermatomyositis-like, polymyositis, and overlap syndrome.^{3,8,21} Peer review reports of IMM in horses are limited.^{6,7,9,22} Causes of IMM in horses have not been fully elucidated, but temporal relationships have been ascribed to autoimmunity developed to bacterial or viral antigens.^{6,9,17,22} To our knowledge, there is limited information published about clinical outcome, physical examination findings at presentation, and treatment of horses with IMM. Outcome, prognostic indicators, and impact of treatments have not been reported to the author's knowledge. Therefore, the objective of the study was to determine whether hospital outcome was associated with clinical or laboratory findings, therapeutic modalities, or hospitalization time. Specifically, associations of muscle enzyme elevations and concurrent illness(es) with hospital outcome were investigated.

Materials and Methods

Case Selection

Medical records from the William R. Pritchard Veterinary Medical Teaching Hospital (VMTH) and the Neuromuscular Disease Laboratory (NDL) at UC Davis were searched between the years of 1991–2014 using the key words: inflammatory myopathy, immune-mediated myositis, and myositis. Horses with records of skeletal muscle biopsies were selected. The inclusion criteria consisted of having a definitive diagnosis of IMM based on histological findings on a muscle biopsy defined as the presence of lymphocytic infiltration within myofibers, perimysial, epimysial, and perivascular areas; and myonecrosis. Muscle specimens were further analyzed to determine populations of B- and T-lymphocytes. Cases were excluded if pathogens such as bacteria or parasites were observed in the muscle specimen examined.

Data Acquisition

Information obtained from medical records included signalment, onset of clinical signs, physical examination findings, CBC, and chemistry panel performed at the time of admission, treatment, duration of hospitalization, and outcome. Long-term follow-up information was located within the medical record or obtained by telephone communication with the owner, trainer, or referring veterinarian.

Electromyography

Electromyography (EMG) was offered as part of the diagnostic work-up for muscle disease in horses after the year of 2000. However, only six owners consented to the study. Electromyography was performed using two machines upon availability (Viking IVD^a, VikingQuest^b). A concentric needle electrode (26 gage by 50 mm length, recording area of 0.07 mm²)^c was used to perform the EMG, and a subdermal needle electrode (30G by 20 mm)^d served as the ground. The muscles evaluated included the *triceps brachii*, *supraspinatus*, *infraspinatus*, *lumbar paraspinalis*, *gluteus medius*, *quadriceps femoris*, and *semimembranosus* muscles. To avoid further damage to the muscles by the insertion of the EMG needle, only one side of the horse was evaluated and three sites per muscle were examined. Observed abnormalities were classified according to a published grading system.²³

Muscle Biopsy

Equine muscle biopsy specimens received at the NDL were snap frozen in isopentane, precooled in liquid nitrogen, and stored at –80°C until further processing. Muscle specimens at the NDL were routinely processed for histological and immunohistochemical analysis and evaluated under light microscopy as previously described.²⁴ In brief, the following histochemical stains and reactions were performed: hematoxylin and eosin, modified Gomori trichrome, periodic acid Schiff, phosphorylase, esterase, staphylococcal protein A-horseradish peroxidase, myosin ATPase at preincubation pH of 9.8, 4.6, and 4.3, nicotinamide adenine dinucleotide, succinate dehydrogenase, acid phosphatase, alkaline phosphatase, and oil red O. Immunohistochemistry to determine the type of inflammatory cells included clusters of differentiation for B-lymphocytes (CD20+, CD79+), T-lymphocytes (CD3+, CD4+, CD8+), and macrophages (CD11c+). All stains and reactions previously mentioned were performed in samples collected from 1999 to 2014 (n = 48 horses). Archived muscle biopsies from two healthy horses were used as negative controls for immunophenotyping. For early recognition of suspected IMM, hematoxylin and eosin were performed on muscle biopsies from 30 horses on the day of biopsy.

Statistical Analysis

Initially, Fisher's exact test was used to compare categorical variables, and the exact Mann-Whitney test was used to compare continuous variables between horses that either died or were euthanized because of a poor medical prognosis based on clinicians' criteria (nonsurvivors) and horses discharged alive (survivors). For those variables with a significant association ($P < .05$), exact logistic regression was then used to quantify the magnitude of the association using odds ratios and 95% confidence intervals. Horses that were euthanized for solely financial reasons were excluded from prognosis analyses. All analyses were performed with standard software (Stata 1C/13.1^e and LogXact-11^f).

Results

Animals

Sixty-eight horses met the inclusion criteria. Fifty-two (76%) of the 68 horses in this study were Quarter horses or related breeds. Other breeds included Thoroughbreds (14%), Warmbloods (8%), and Arabians (2%). The sex distribution of all horses consisted of 33 females, 27 geldings, and eight intact males. The sex distribution for Quarter horses and related breeds was 27 females, 19 geldings, and eight intact males. Mean age at the time of initial examination at the VMTH was 5 years (range, 3 months to 23 years). The mean age of Quarter horses and related breeds at initial examination was <4 years old (range of 3 months–21 years), whereas in other breeds, the average age was >10 years old (range of 1–23 years). Median hospitalization time was 7 days (range, 3–26 days). Reported historical events before the development of IMM included respiratory infection within days to weeks (n = 19/68, 28%), and vaccination within 3–4 weeks against influenza and herpes virus-1 (n = 13/68, 19%). Pathogens identified through microbial culture or PCR or both causing concurrent or recent infection included *S. equi equi* (n = 5), *S. equi zooepidemicus* (n = 4), *C. pseudotuberculosis*

(n = 3), *Anaplasma phagocytophilum* (n = 3), equine herpes virus-1 (n = 3), and equine influenza virus (n = 1). The most common clinical signs consisted of rapidly progressive diffuse symmetrical muscle atrophy (n = 55/68, 80%) and stiff gait (n = 50/68, 74%). Other common sign included fever in 44% of the horses (n = 30/68; median 101.3°F [38.5°C], range 101–104°F [38.3–40°C]; reference range 99–100.8°F [37.2–38.2°C]). Recumbency was recorded in 8% of the horses (n = 6/68).

Clinicopathologic data

White blood cell (WBC) counts were above the reference range in 60% of the horses (n = 41/68). Elevated muscle enzyme activities (CK and AST) were identified in 97% of the horses (n = 66/68) at the time of admission (Table 1). Other laboratory parameters are also shown in Table 1. Troponin I was measured in two Quarter horses with suspected cardiomyopathy based on persistent tachycardia (60–80 bpm) during hospitalization and found increased (>0.17 and 0.35 ng/mL; reference range 0.01–0.07 ng/mL). Troponin I was within reference value at the time of discharge.

Electromyography

Six of 68 horses had an electromyographic examination. These horses had nonspecific abnormalities consisting of mild-to-moderate increased insertional activity, fibrillation potentials (amplitude 50–200 μ V, duration 0.5–3 msec), and positive sharp waves (amplitude 50 μ V to 4 mV; duration <5 msec) in multiple muscles examined.

Muscle Biopsy

As part of the inclusion criteria, all muscle specimens examined had mononuclear cell infiltration that was

Table 1. Clinicopathologic data obtained at the time of admission. N = number of horses with variable above reference range/total number of horses evaluated for such variable.

Variable	Median (range)	Reference Range
WBC count (cells/ μ L) n = 41/68	13,697 (4,720–21,600)	5,000–11,600
Fibrinogen (mg/dL) n = 24/47	500 (100–800)	100–300
SUN (mg/dL) n = 14/47	27 (7–72)	12–27
Creatinine (mg/dL) n = 8/47	1.5 (0.6–72)	0.9–2.0
Calcium (mg/dL) n = 11/47	11.1 (8.2–14.3)	11–14
Potassium (mEq/L) n = 0/47	3.8 (2.4–5.3)	3–5.5
AST (U/L) n = 66/68	12,270 (112–56,129)	165–495
CK (U/L) n = 66/68	101,071 (129–1,456,218)	120–287

predominantly lymphocytic. Of 68 horses, 45 horses had more than one muscle collected for histologic evaluation. Muscle biopsies were taken predominantly from the *gluteus medius* muscles (n = 45/68 horses, 66%). Other muscles included the *semimembranosus* (60%), *sacrocaudalis dorsalis lateralis* (30%), *triceps brachialis* (10%), and *masseter* (4%). Immunophenotyping through clusters of differentiation were performed in muscle biopsies from 18 horses. Lymphocytic cellular infiltration was present around blood vessels in 66.7% of muscle specimens examined, and within endomysial and perimysial areas in 88.9% (Fig 1A). Lymphocytic infiltration was predominantly CD4+ T-lymphocytes, followed by CD8+ T-lymphocytes. CD20+ B-lymphocytes were observed in 39% of the cases (Fig 1B). Macrophages, identified histologically and through acid phosphatase enzymatic reaction and immunophenotyping (CD11c+), were observed in areas of myonecrosis affecting all fiber types. These abnormalities had a multifocal coalescing to diffuse distribution throughout the muscle specimen.

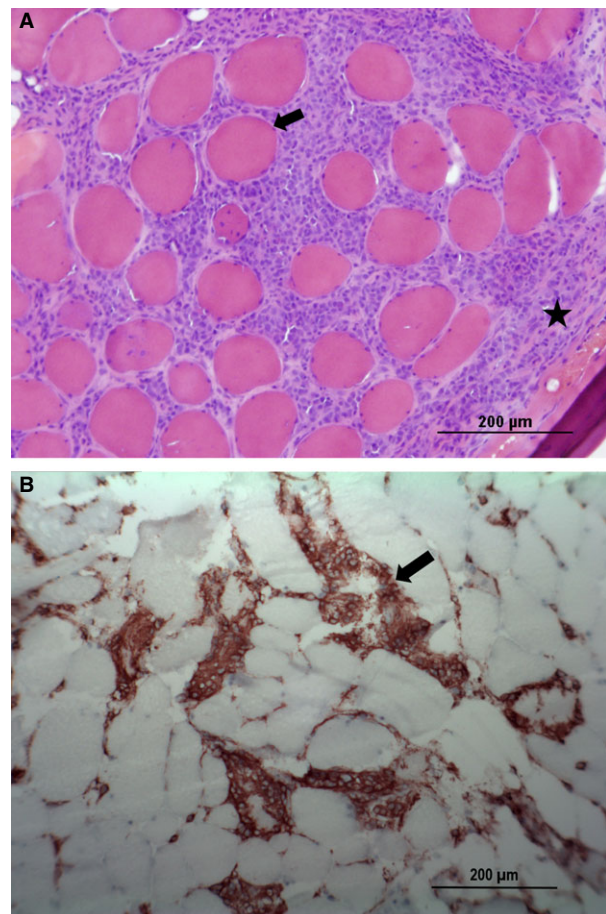


Fig 1. (A) Lymphocytic and macrophages cellular infiltration within endomysial (arrow) and perimysial (star) areas of *gluteus medius* muscle shown on hematoxylin and eosin at 10 \times , bar = 200 μ m. (B) Lymphocytic cellular infiltration consisting of CD4+ T-lymphocytes (arrow) based on immunophenotyping of *gluteus medius* muscle at 10 \times , bar = 200 μ m.

Outcome and Follow-Up

Of the 68 horses included in the study, 59 (87%) survived to discharge, one (1%) died, eight (12%) were euthanized. All horses that were treated medically (supportive care with fluids administered IV, antimicrobials for those with concurrent or suspected infection, with or without corticosteroids) within 24 hours of admission to the VMTH survived to discharge (59/68 horses). Twenty-eight horses were treated with corticosteroids, and all survived to discharge. Corticosteroids used were dexamethasone (0.05–0.1 mg/kg IV once or for a few days with tapering dosages of 25% decreases in some cases and then followed by oral prednisolone at 1 mg/kg with tapering dosages as explained next under prednisolone) and prednisolone (1 mg/kg PO q24h followed by tapering dosages of 20–25% decreases over days to weeks [2–6 weeks]).

Factors evaluated for their association with survival to discharge are shown in Table 2. Concurrent illness alone was not a significant prognostic indicator; however, horses with concurrent fever and an additional illness had a significantly decreased survival. Other specific factors such as presentation during winter season, being a non-Quarter horse, AST, and having a presumptive diagnosis of immune-mediated myositis upon hospital admission were also significantly associated with outcome.

Long-term follow-up information (6 months after hospital discharge) was available for 59 horses. Nineteen (32%) horses, all of Quarter horse breed ($n = 19/52$; 37%), had a recurrence of IMM within 6 months of hospital discharge. Of these, 17 (90%) survived 3 months past the second IMM episode, whereas two (10%) did not survive the second episode. Fifty-seven (84%) horses were reported healthy by 6 months after hospital discharge. All surviving horses that had muscle atrophy during hospitalization regained their muscle mass within 3–6 months. Both horses that did not survive the second episode of IMM were in chronic renal failure that resulted from an acute insult that developed during the first episode of IMM.

Discussion

This report demonstrates that horses with immune-mediated myositis have a high survival rate. Concurrent illness together with fever was significantly associated with nonsurvival, although concurrent illness or fever alone were not. Acute renal failure could have been a result of the combination of pigment nephropathy due to the deposition of myoglobin in conjunction to nonsteroidal anti-inflammatory drug administration and dehydration before referral. Rhabdomyolysis and acute renal failure occur in humans.²⁵ Although there was no specific concurrent illness or history associated with the development of IMM, clinical signs observed in these horses were similar to those described in a previous study.⁶ Clinical signs commonly observed in both studies were a stiff gait, lethargy, and muscle atrophy most notably over the epaxial, gluteal, and neck/shoulder muscles developing within the first few days of hospitalization.

Although medical treatment was used in all horses that survived to discharge, it was not the goal of this study to evaluate the relative efficacy of treatments due to the retrospective study design and the potential for confounding by clinical indication. It should be sufficient to note that prompt therapy was associated with a favorable prognosis.

In this study, all horses evaluated through an EMG study had nonspecific alterations consisting of prolonged insertional activity, fibrillation potentials, and positive sharp waves. These abnormalities occur in humans and dogs with inflammatory myopathies.^{26–28} Fibrillation potentials and positive sharp waves arise from spontaneously firing hypersensitive myofibers as the result of destabilization of the sarcolemmal membrane.²³ Therefore, these abnormal findings are not exclusive of inflammatory myopathies and can also be observed in neuropathies and other myopathies.²³ Further, due to the low number of cases examined through an EMG in this study, there is a potential for bias.

Identifying definitive causes of the development of IMM in these horses was not a goal of this study, nor could it be due to the study's retrospective cohort design. However, a possible association between previous respiratory infection and vaccination was suspected in 38% of the cases. Quarter horses and related breeds appeared to be over-represented (76% of cases); however, this assumption cannot be definitively made because the distribution of breeds in the source population of cases is unknown. Further, Quarter horses and related breeds were younger than other breeds (mean age < 4 years versus > 10 years, respectively). The pathophysiology for the development of IMM in humans has been presumed to be due to the lack of self-tolerance to antigens expressed by muscle cells, activation of T-lymphocytes by shared epitopes with infectious agents causing antigenic mimicry, microbial superantigens, and high concentration of local cytokines.^{1,2,29} The exact mechanism of disease in the horse is unknown but possibly involves a similar mechanism of loss of self-tolerance to antigens expressed by muscle cells, resulting in the development of autoimmunity against its own muscle cells. Based on the results of the present study, the authors speculate that this suspected autoimmunity can occur within days to weeks (up to 4 weeks) after the exposure to pathogens (bacterial, viral) and other antigens (presumably peptides contained in vaccines) in some cases. A possible association between autoimmunity and breed predisposition has been considered.⁶ Pathogens associated with disease in the present study included *S. equi equi*, *S. equi zooepidemicus*, *C. pseudotuberculosis*, *Anaplasma phagocytophilum*, equine herpes virus-1, and equine influenza virus. Vaccines suspected to be associated with IMM included influenza and herpes virus-1. Rhabdomyolysis associated with influenza virus natural and experimental infection occur in humans and mice, respectively.^{25,30}

Based on immunophenotyping, predominant CD4+ followed by CD8+ T-lymphocytes, a cellular immune response was responsible for the observed myonecrosis. This finding was similar to that described in previous

Table 2. Factors hypothesized to be associated with survival to discharge in 68 horses with IMM.

Variable	Horses (n)	Fisher's exact <i>P</i> -value	Odds ratio	95% Confidence interval	Logistic regression <i>P</i> -value
History					
Winter season (vs all others)	68	.014	8.19	1.23–55.31	.028
Year	68	.119			
Housing (stall vs pasture)	30	1.000			
Vaccination history (positive)	68	1.000			
Signalment					
Age (1 year)	68	.311			
Breed (Quarter horse)	37		1.00	–	–
Breed (nonQuarter horse)	16	.008	15.35	1.50–794.28	.011
Breed (Quarter horse-related)	15		8.55	0.62–485.10	.1
Sex (female)	33				
Sex (gelding)	27	1.000			
Sex (intact male)	8				
Weight (×100 kg)	21	.153			
Physical examination					
Temperature (1°F)	67	.564			
Fever present	68	.253			
Concurrent illness present	68	.189			
Fever and concurrent illness	68	.033	8.07	0.98–379.19	.041
Edema present	40	.233			
Vasculitis present	36	.691			
Lameness present	68	1.000			
Lameness grade (1 unit increase)	67	.431			
Neurologic deficits present	68	.340			
Neurologic grade (1 unit increase)	67	.634			
Laboratory					
WBC (×1,000 cells/μL)	67	.944			
Fibrinogen (×100 mg/dL)	67	.867			
AST (×1,000 U/L)	67	.013	0.85	0.68–0.98	.01
CK (×10,000 U/L)	67	.176			
Creatinine (mg/dL)	67	.118			
SUN (×10 mg/dL)	67	.831			
Calcium (mg/dL)	67	.278			
Potassium (mEq/L)	66	.753			
Muscle biopsy					
Early presumptive diagnosis on admission	66	.003	10.12	1.79–74.35	.005
Treatment					
Steroid therapy	68	.151			

studies in horses.^{6,9} In our study, CD20+ B-lymphocytes were not a major component of this suspected autoimmunity. Further, staphylococcal protein A-horseradish peroxidase for the detection of IgG antibodies in the muscle cell membrane did not reveal antibody staining. Myonecrosis resulted in the elevation of muscle enzyme activities (median: AST 12,270 U/L, CK 101,071 U/L). Lewis et al.⁶ described IMM in horses as having increased muscle enzyme activity with persistently high concentrations of AST (>1,000 U/L) and CK (>10,000 U/L) and ascribed it to chronic and active myofiber destruction. Despite marked increases in muscle enzyme activities, AST and CK were not a useful prognostic indicator for outcome in our study. Cardiomyopathy was presumed to be associated with IMM, but this was not confirmed histologically because the two horses fully recovered. Many of the horses (78%) had a concurrent infection within various body systems, including respiratory and gastrointestinal systems. Importantly, the presence of a suspected bacterial, viral, or parasitic infection was not associated with decreased survival.

Additionally, horses with infections were treated with corticosteroids in this study population. Long-term prognosis for horses with IMM based on a 6-month follow-up information is favorable. However, one-third of horses in this study had a recurrent episode within 6 months of the initial presentation. Prognosis from the second IMM episode was also favorable. A causative agent, disease, or illness could not be attributed to the IMM recurrence. Horses that did not survive the second IMM episode had evidence of chronic renal failure that was unresponsive to IV fluid diuresis. These horses had acute renal failure during their initial IMM and subsequent renal damage during their second episode. The azotemia associated with these nonsurvivors was attributed to myoglobin nephrosis (histologically confirmed) secondary to myonecrosis associated with IMM.

In conclusion, IMM is a cause of apparent muscle pain, stiffness, and rapid muscle atrophy that occurs within days due to marked rhabdomyolysis as evidenced by elevated muscle enzyme activities. Horses with IMM might present with fever, leukocytosis, and

hyperfibrinogenemia. Monitoring of renal variables is important because renal insult resulting in failure is a potential complication. Although IMM can occur in horses of various breeds, Quarter horses and related breeds seem to be predisposed.^{6,9} Therefore, a familial or genetic bases for the development of disease must be considered in this breed. Electromyographic alterations are observed in affected horses. Immune-mediated myositis can have a favorable outcome if clinical signs are recognized early and treatment with corticosteroids is initiated promptly along with supportive care and treatment of any concurrent illness including antimicrobial therapy for those horses with concurrent bacterial infection. However, horses that presented with concurrent fever and an additional illness had diminished survival. Muscle mass recovery might take 3–6 months after the insult, and return to work is possible. Quarter horses might suffer from recurrent episodes of IMM.

Footnotes

- ^a Viking IVD, Nicolet Biomedical Inc., Madison, WI
^b VikingQuest, Nicolet Biomedical Inc., Madison, WI
^c Disposable concentric needle electrode, VIASYS Healthcare, Madison, WI
^d Subdermal Grass electrode, Astro-Med Inc., West Warwick, RI
^e Stat 1C/13.1, StataCorp. LP, College Station, TX
^f LogXact-11, Cytel Software Corporation, Cambridge, MA
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Conflict of Interest Declaration: Authors declare no conflict of interest.

Off-label Antimicrobial Declaration: Authors declare no off-label use of antimicrobials.

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