JOURNAL OF
Veterinary Emergency
AND Critical Care

Retrospective Study

Journal of Veterinary Emergency and Critical Care **00**(0) 2016, pp 1–6
doi: 10.1111/vec.12529

Use of Yunnan Baiyao and epsilon aminocaproic acid in dogs with right atrial masses and pericardial effusion

Lisa A. Murphy, DVM; Cynthia M. Panek, DVM, DACVIM; Domenico Bianco, DVM, PhD, DACVIM and Reid K. Nakamura, DVM, DACVECC, DACVIM

Abstract

Objective – To describe the utility of Yunnan Baiyao (YB) alone or in combination with epsilon aminocaproic acid (EAC) for the treatment of dogs with echocardiographically identified right atrial (RA) masses and pericardial effusion (PE).
Design – Retrospective case-controlled study.
Setting – Two private practice referral hospitals.
Animals – Client-owned dogs with RA masses and PE identified echocardiographically over a 3-year period.
Interventions – None.
Measurements and Main Results – There were 67 dogs identified with RA masses and PE during the study period. Sixteen dogs were treated with YB alone while 8 dogs were treated with YB in combination with EAC in addition to pericardiocentesis. Forty-three dogs were treated with pericardiocentesis alone and were considered to be the control group. There was no difference between the groups in regards to signalment, physical examination abnormalities, and diagnostic test results on presentation. There was no significant difference between the 2 groups with respect to number of pericardiocenteses performed and there were no side effects attributed to the YB or EAC in any of the dogs. Median time to recurrence of clinical signs was not significantly different between the treatment (12 d, range 1–186 d) and control group (14.5 d, range 1–277 d). The median survival of dogs treated with YB alone or in combination with EAC (18 d, range 1–186 d) was also not significantly improved compared to dogs treated with pericardiocenteses alone (16 d, range 1–277 d).
Conclusions – This study suggests YB alone or in combination with EAC is relatively safe but does not significantly delay recurrence of clinical signs or improve survival in dogs with RA masses and PE. Due to the small cohort size, further prospective studies evaluating these drugs and their effects on hemostasis in dogs with RA masses and PE are warranted.

(J Vet Emerg Crit Care 2016; 00(0): 1–6) doi: 10.1111/vec.12529

Keywords: antifibrinolytic, canine, hemangiosarcoma, hemostasis, procoagulant, therapy

Abbreviations

EAC epsilon aminocaproic acid
HSA hemangiosarcoma
PE pericardial effusion
RA right atrial/atrium
YB Yunnan Baiyao

From the Oradell Animal Hospital, Paramus, NJ 07652 (Murphy); United Veterinary Specialty and Emergency, San Jose, CA 95123 (Panek); Advanced Critical Care, Emergency and Specialty Services, Woodland Hills, CA 91364 (Bianco); and Veterinary Specialty and Emergency Center, Thousand Oaks, CA 91360 (Nakamura).

This study was performed at Southern California Veterinary Specialty Hospital and VCA Advanced Veterinary Care Center.

The authors declare no conflicts of interest.

Address correspondence and reprint requests to
Dr. Reid K. Nakamura, Veterinary Specialty and Emergency Center, 2967 North Moorpark Road, Thousand Oaks, CA 91360, USA.
Email: r.kiyoshi.nakamura@gmail.com
Submitted October 16, 2014; Accepted March 17, 2015.

Introduction

Pericardial effusion (PE) in dogs is most commonly secondary to underlying neoplasia with the right atrium (RA) and heart base the most common sites for masses to be identified.[1–7] When a mass is identified originating from the RA, hemangiosarcoma (HSA) is by far the most common histopathologic diagnosis although other neoplasms are occasionally identified including neuroendocrine tumors, thyroid gland adenocarcinoma, mesothelioma, and lymphoma.[6,7] While

pericardiocentesis can relieve the symptoms, the hemorrhagic PE frequently rapidly recurs and the median survival time reported is consistently less than 30 days.[1–7] Consequently, further treatment options have been investigated including pericardiectomy,[1] thorascopic pericardiectomy,[8] surgical resection of the RA mass with or without adjuvant chemotherapy,[5] and doxorubicin-based chemotherapy alone.[9] However, surgery is typically expensive, invasive, and frequently associated with complications, while doxorubicin-based chemotherapy is commonly associated with side effects as well.[5,8,9]

Yunnan Baiyao (YB) is a well-known Chinese herbal remedy utilized to reduce bleeding by either topical or oral administration. It was developed in the Yunnan province in China in the early 1900s and its hemostatic properties were first utilized on a large scale by Chinese soldiers in World War II.[10–14] Following administration in human and animal studies, significant decreases in bleeding and clotting times were observed.[10–14] Several human studies have shown that YB can reduce bleeding in patients with different types of cancers and ulcerative diseases when used in conjunction with conventional hemostatic interventions.[15,16] The proposed mechanism is enhanced expression of surface glycoproteins on platelets under conditions of stimulation, which shortens bleeding and clotting times.[10,11,17,18] In addition, YB has been found to induce dose- and time-dependent canine HSA cell death in vitro through initiation of caspase-mediated apoptosis.[19]

Epsilon aminocaproic acid (EAC) is classified as an antifibrinolytic that prevents activation of plasminogen into plasmin thereby inhibiting the dissolution of fibrin clots. A recent veterinary study demonstrated that EAC decreased the prevalence of postoperative bleeding in retired racing Greyhounds undergoing gonadectomy by increasing clot strength and reducing fibrinolysis.[20] A meta-analysis of antifibrinolytic use in people concluded their use can reduce blood loss and the need for red blood cell transfusions after surgery.[21] As such, YB alone or in combination with EAC could represent an ideal medical option for dogs with RA masses and PE by preventing recurrence of hemorrhagic PE. The purpose of this study was to retrospectively evaluate YB and EAC use in dogs with RA masses and PE identified echocardiographically and to determine if their use would increase the time to recurrence of clinical signs or improve long-term survival compared with a cohort of dogs that these not receive these agents but had been identified with a mass in the RA and PE.

Materials and Methods

The medical records database was searched for all dogs that presented with PE between August 1, 2011 and August 1, 2014 at 2 large specialty hospitals around a large urban city. For inclusion into the study, dogs had to be diagnosed with an RA mass and identified to have PE on the basis of echocardiography. The echocardiogram had to be performed by a board-certified cardiologist or cardiology resident under the supervision of a board-certified cardiologist. Dogs did not need to have a histological diagnosis of the RA mass as HSA for inclusion into the study. Dogs were included in the treated group if they were administered YB[a] or EAC[b] subsequent to diagnosis, while dogs were included in the control group if they received no therapy other than pericardiocentesis for the PE. As this is a retrospective study, owner consent was not sought at the time of treatment for any of the dogs. However, the fact that YB is a Chinese herbal remedy of unknown efficacy was disclosed to clients at the time of prescribing by the attending clinician.

Dogs were excluded from the study if the echocardiogram was either not performed by a board-certified cardiologist or cardiology resident, or if a mass was not identified originating from the RA, RA appendage, or right atrio-ventricular groove. Any dog that had any type of cardiac surgery such as pericardiectomy or RA mass resection or if the dog had a pericardiocentesis performed prior to presentation was excluded as well. In addition, dogs that received any type of chemotherapy for treatment of the RA mass were excluded from the study. Finally, dogs could not receive medication that could interfere with primary or secondary hemostatic function such as aspirin, clopidogrel, heparin, or warfarin. Data collected from the medical record included signalment, clinical signs, physical examination findings, diagnostic test results, dose of YB and EAC utilized, total number of pericardiocenteses performed and the volume of effusion obtained from each pericardiocentesis, time to recurrence of clinical signs, and long-term survival. Tachycardia was defined as a heart rate >160/min and tachypnea as a respiratory rate >60/min. Pulsus paradoxus and determination of weak pulses were discerned by subjective palpation of the femoral pulse. The presence or absence of ascites was determined via ultrasonography during the initial echocardiographic exam. When long-term survival and time to recurrence of clinical signs were not available in the medical record, follow-up phone calls were made to the referring veterinarian or to the owner of the dog. Survival data and time to recurrence of clinical signs were calculated from the date of discharge from the hospital after identification of the RA mass on echocardiography and initiation of YB or EAC therapy. Primary endpoints of the study were time to recurrence of clinical signs and long-term survival from discharge. Secondary end points included tolerability and possible side effects attributed to the YB and EAC, which were

Table 1: Diagnostic results and treatment of dogs with right atrial masses and pericardial effusion in control and treated groups

Characteristic	Control group ($n = 43$)	Treated group ($n = 24$)	*P* value
Thoracic radiographic abnormalities	Globoid cardiac silhouette: 9/14 (64%)	Globoid cardiac silhouette: 9/15 (60%)	0.89
	Suspicion of metastatic disease: 0/14 (0%)	Suspicion of metastatic disease: 3/14 (21%)	0.78
	Pleural effusion: 3/14 (21%)	Pleural effusion: 3/14 (21%)	1.0
Electrocardiographic abnormalities	Sinus tachycardia: 8/25 (32%)	Sinus tachycardia: 3/7 (42%)	0.81
	Ventricular premature contractions: 8/25 (32%)	Ventricular premature contractions: 4/7 (57%)	0.44
	Electrical alternans: 3/25 (12%)	Electrical alternans: 0/7 (0%)	0.85
Volume of pericardial effusion removed	6.1 mL/kg (0.12–34.4 mL/kg)	6.06 mL/kg (1.43–23.16 mL/kg)	0.91
Total number of pericardiocenteses performed per dog	1 tap per dog (range 1–3 taps per dog)	1 tap per dog (range 1–6 taps per dog)	1.0
Time to recurrence of clinical signs	14.5 days (range 1–277 d)	12 days (1–186 d)	0.82
Long-term survival	16 days (range 1–277 d)	18 days (range 1–186 d)	0.70

determined via communication with the owners and their subjective assessments.

Statistical Analysis

Data from the dogs in the 2 groups were compared by use of a Student's *t*-test for data with normal distribution, and a Mann–Whitney rank sum test was used for data with nonnormal distribution. The Kaplan–Meier estimates of the distribution of times from diagnosis to death were computed, and the Mantel–Cox log-rank analysis was performed to compare the survival curves between the 2 groups. Results are presented as median and range unless indicated otherwise. Statistical analyses were performed using a standard statistical software package.[c] For all analyses, P values <0.05 were considered statistically significant.

Results

During the study period, 24 dogs were treated with YB and 8 of these dogs were simultaneously treated with EAC. No dogs were treated with only EAC during the study period. These 24 dogs constituted the treated group. A total of 43 dogs with an echocardiographically identified RA mass and PE were identified during the same time period and were treated with pericardiocentesis alone. This group of dogs was designated the control group. Thirteen dogs during the study period were treated with some type of chemotherapy and 4 dogs underwent pericardiectomy and all were excluded from analysis.

Breeds represented in the control group include Golden Retrievers ($n = 15$), mixed breed dogs ($n = 9$), and 1 dog each of the following breeds: Jack Russell Terrier, Collie, Rottweiler, Doberman, Bichon Frise, Pit Bull, Cairn Terrier, Akita, Vizsla, Labrador Retriever, West Highland White Terrier, Miniature Pinscher, German Shepherd Dog, Belgian Malinois, English Setter, Bull Mastiff, Beagle, Pug, and Boxer. Breeds in the treated group included mixed breed dogs ($n = 8$), Golden Retriever ($n = 7$), Labrador Retriever ($n = 2$), German Shepherd Dog ($n = 2$), and 1 each of the following breeds: Yorkshire Terrier, Beagle, Portuguese Water Dog, Anatolian Shepherd, and West Highland White Terrier. The median age of dogs presented was 149 months (range 66–220 mo) in the control group and 132 months (range 59–192 mo) in the treated group. There was no statistical difference between groups with regard to age, sex, or body weight between the 2 groups. Presenting complaints included lethargy (37/43 and 20/24), collapse (12/43 and 13/24), coughing (9/43 and 3/24), decreased appetite (10/43 and 11/24), and tachypnea (11/43 and 8/24). Physical examination findings included muffled heart sounds (25/43 and 12/24), tachycardia (25/43 and 3/24), tachypnea (13/43 and 10/24), pale mucous membranes (16/43 and 5/24), weak pulses (28/43 and 10/24), pulsus paradoxus (8/43 and 4/24), and ascites (12/43 and 7/24). There was no significant difference between the 2 groups in regards to frequency of the presenting complaints or physical examination abnormalities.

Thoracic radiographs were performed in 14 dogs in the control group and 15 dogs in the treated group while electrocardiography was performed in 25 dogs in the control group and 7 dogs in the treated group. There was no statistical difference in regards to frequency of abnormalities identified on thoracic radiographs or electrocardiography between the 2 groups (Table 1). The volume of PE evacuated was not significantly different nor was the median number of pericardiocenteses performed per dog statistically different between the 2 groups (Table 1).

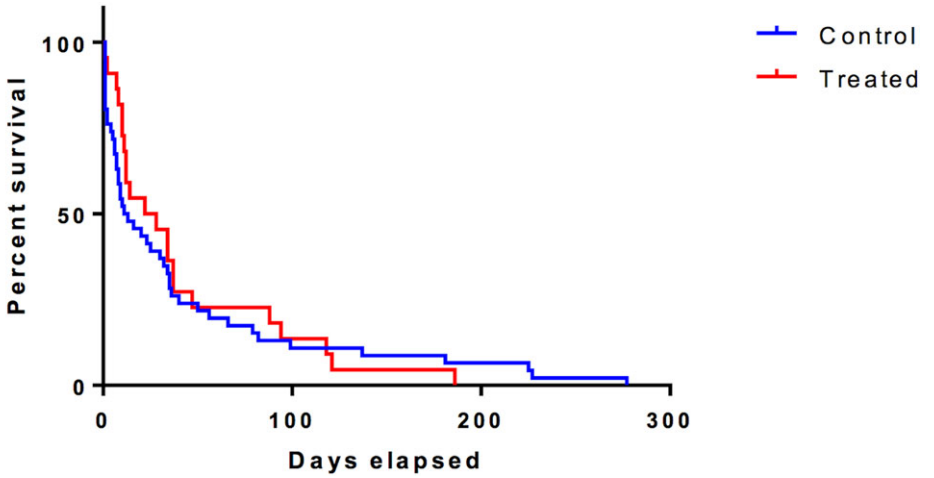

Figure 1: Kaplan–Meier survival curves comparing dogs with right atrial masses and pericardial effusion treated with pericardiocenteses alone (control group; blue line) versus pericardiocentesis in addition to treatment with Yunnan Baiyao with or without epsilon aminocaproic acid (treated group; red line) showing no significant improvement in survival.

An empirical dosage of YB of 1 capsule orally twice daily was utilized in 18 dogs, 2 capsules orally twice daily in 5 dogs, and 2 capsules orally 3 times a day in 1 dog. Eight dogs received EAC at a median dosage of 48.8 mg/kg (range 43.0–66.6 mg/kg) and were given EAC 3 times a day in 6 dogs and 4 times a day in 2 dogs.

The median time to recurrence of clinical signs in the treated group (12 d, range 1–186 d) was not significantly different from the control group (14.5 d, range 1–277 d). By the end of the study period, all dogs in the control group and all but 1 dog in the treated group had died. Cause of death in the treated group was euthanasia due to recurrence of clinical signs ($n = 16$), died at home ($n = 6$), and euthanasia due to respiratory distress ($n = 1$). Cause of death in the control group was euthanasia due to recurrence of clinical signs ($n = 30$), euthanasia no cause recorded ($n = 7$) and died at home ($n = 6$). The median survival time of dogs in the treated group (18 d, range 1–186 d) was not significantly improved compared to the control group (16 d, range 1–277 d; Table 1, Figure 1). The median survival of the 8 dogs that received YB and EAC (17 d, range 1–88 d) was also not significantly improved compared to the 16 dogs that received YB alone (31 d, range 1–186 d). There were no side effects attributed to the YB or EAC use in any dogs during the study period.

Discussion

The primary findings of this study suggest that there were no significant delay in recurrence of clinical signs nor improvement in survival in dogs with RA masses and PE treated with YB alone or in combination with EAC. The median survival time of 18 days for dogs receiving YB and EAC in this study was not significantly improved compared to the control group and is also similar to previous studies of dogs with RA masses and PE treated with pericardiocentesis alone.[1–7]

The authors found varying dosages recommended for YB but none has been published in a peer review literature. The most frequent dosage utilized was 1 capsule orally twice daily and the authors suspect the reasoning behind this dosage was because YB comes in a 16 capsule packet and owners were instructed to recheck in 1–2 weeks. As such, 1 capsule twice daily requires only 1–2 packets of YB be dispensed for the dog to have sufficient medications until the recheck examination. YB was recently found to induce dose- and time-dependent canine HSA cell death in vitro through initiation of caspase-mediated apoptosis.[19] This study demonstrated that the average inhibitory concentration of YB for 3 different canine HSA cell lines was 350.17 μg/mL.[19] However, it is unclear how many capsules per day would be required to attain this inhibitory concentration in dogs. Furthermore, while YB has proven hemostatic properties, its exact compositional formula is a closely guarded secret by the manufactures and like many nutritional supplements, is not subjected to any quality control measures as compared to pharmaceuticals. This potential for compositional inconsistency was highlighted by a recent study evaluating nutrient and metal concentration of several Chinese herbal remedies including YB revealing a significant variation in the mineral content of the same remedy when obtained from different sources.[22]

EAC was used in approximately one-third of the treatment group dogs in this study as well so the ability to evaluate its effectiveness is low. The dosage of EAC utilized in the dogs in this study was approximately

twice that of the dosage utilized to reduce bleeding in the retired racing greyhounds after gonadectomy at the same frequency.[20] Despite this, EAC did not provide any measureable improvement in survival compared to YB alone and the prognosis for all dogs remained poor. More recently it was found that dogs are hyperfibrinolytic compared with people and may require higher doses of EAC to completely inhibit fibrinolysis in dogs.[23] The optimal dose of EAC to reduce clinical bleeding in dogs requires further evaluation.

The YB and EAC appeared well tolerated in the dogs in this study as there were no side effects attributed to either therapy reported by the owners or identified by the primary clinicians. Other studies evaluating EAC use in dogs also did not identify any adverse effects.[20] There are no reports of any adverse effect of YB use in dogs in the veterinary literature. However, given the short duration of survival of almost all dogs in the study it is difficult to assess tolerability and safety of YB or EAC as the dogs may simply have not lived enough to develop drug-related side effects.

Ideally, dogs in this study would have had hemostatic function assessed before and after YB and EAC administration with thromboelastography or platelet aggregometry to determine if there was any measureable improvement in hemostatic function. However, such tests were not available at either hospital during the study period. As such, the authors are unable to determine if YB and EAC produce an improvement in measureable hemostatic parameters when no clinical improvement was observed.

Limitations to the study are inherent to the retrospective design, and include lack of blinding or randomization, lack of confirmatory diagnosis, lack of standardized dosing and the empirical nature of YB dosing, lack of standardized EAC dosing, lack of hemostatic analysis of patients, lack of complete staging, and small sample size. None of the dogs in this study had histologic confirmation of the suspected RA HSA. Survival data are also affected as no limit was placed on the number of pericardiocenteses allowed to be performed on dogs included in either group. Furthermore, a small number of animals in this group had a high number of repeat pericardiocenteses performed which would also affect overall survival time. A previous study has reported that 88% of RA masses are histologically confirmed to be HSA, but other tumors were identified as well.[7] The effect of YB and EAC on different histological RA tumors is unclear.

Conclusions

Prognosis of dogs with RA masses and PE treated with YB alone or in combination with EAC was poor and similar to previous reports of dogs treated with pericardiocentesis alone. There is no evidence to support the use of YB or EAC in place of more aggressive therapies such as surgery or doxorubicin-based chemotherapy for dogs with RA masses and PE. Due to the small size of this retrospective study, further prospective studies are warranted evaluating these drugs and their hemostatic effects on animals with RA masses and associated PE.

Footnotes

[a] Yunnan Baiyao Capsules, Yunnan Baiyao Group Corp. Ltd, Kunming, China.
[b] Episolon Aminocaproic Acid Capsules, Compound Central Pharmacy, Los Alamitos, CA.
[c] SPSS 22.0 for Windows, Microsoft, Redmond, WA.

References

1. Kersetetter KK, Krahwinkel DJ, Jr, Mills DL, et al. Pericardectomy in dogs: 22 cases (1978-1994). J Am Vet Med Assoc 1998; 211:736–740.
2. Dunning D, Monnet E, Orton EC, et al. Analysis of prognostic indicators for dogs with pericardial effusion: 46 cases (1985-1996). J Am Vet Med Assoc 1998; 212:1276–1280.
3. Rajagopalan V, Jesty SA, Craig LE, et al. Comparison of presumptive echocardiographic and definitive diagnosis of cardiac tumors in dogs. J Vet Intern Med 2013; 27:1092–1096.
4. Stafford Johnson M, Martin M, Binns S, et al. A retrospective study of clinical findings, treatment and outcome in 143 dogs with pericardial effusion. J Small Anim Pract 2004; 45:546–552.
5. Weisse C, Soares N, Beal MW, et al. Survival times in dogs with right atrial hemangiosarcoma treated by means of surgical resection with or without adjuvant chemotherapy: 23 cases (1986-2000). J Am Vet Med Assoc 2005; 226:575–579.
6. Ware WA, Hopper DL. Cardiac tumors in dogs: 1982-1995. J Vet Intern Med 1999; 13:95–103.
7. MacDonald KA, Cagney O, Magne ML. Echocardiographic and clinicopathologic characterization of pericardial effusion in dogs: 107 cases (1985-2006). J Am Vet Med Assoc 2009; 235:1456–1461.
8. Jackson J, Richter KP, Launder DP. Thorascopic partial pericardectomy in 13 dogs. J Vet Intern Med 1999; 13:529–533.
9. Ghaffari S, Pelio DC, Lange AJ, et al. A retrospective evaluation of doxorubicin-based chemotherapy for dogs with right atrial masses and pericardial effusion. J Small Anim Pract 2014; 55:254–257.
10. Chew EC. Effects of Yunnan Bai Yao on blood platelets: an ultrastructural study. Comp Med East West 1977; 5:169–175.
11. Chew EC. Yunnan Bai Yao–induced platelet release in suspensions of washed platelets. Comp Med East West 1977; 5:271–274.
12. Li NC, Pan BN, Wang HJ, et al. The effect of Yunnan Baiyao on reduction of intraoperative bleeding of the patients undergoing transurethral resection of prostate. Zhonghua Yi Xue Za Zhi 2007; 87:1017–1020.
13. Ogle CW, Dai S, Cho CH. The haemostatic effects of orally administered Yunnan Bai Yao in rats and rabbits. Comp Med East West 1977; 5:155–160.
14. Ogle CW, Dais S, Ma JC. The haemostatic effects of the Chinese herbal drug Yunnan Bai Yao: a pilot study. Am J Chin Med 1976; 4:147–152.
15. Yang B, Xu ZQ, Zhang H, et al. The efficacy of Yunnan Baiyao on hemostasis and anti-ulcer; a systematic review and meta-analysis of randomized controlled trials. Int J Clin Exp Med 2014; 7:461–481.
16. Ladas EJ, Karlik JB, Rooney D, et al. Topical Yunnan Baiyao administration as an adjunctive therapy for bleeding complications in adolescents with advanced cancer. Support Care Cancer 2012; 20:3379–3383.

17. Fan C, Song J, White CM. A comparison of the hemostatic effects of notoginseng and yun nan bai yao to placebo control. J Herb Pharmacother 2005; 5:1–5.
18. Yang B, Xu ZQ, Zhang H, et al. The efficacy of Yunnan Baiyao on haemostasis and antiulcer: a systematic review and meta-analysis of randomized controlled trials. Int J Clin Exp Med 2014; 7:461–482.
19. Wirth KA, Kow K, Salute ME, et al. In vitro effects of Yunnan Baiyao on canine hemangiosarcoma cell lines. Vet Comp Oncol 2016; 14:281–294.
20. Marin LM, Iazbik MC, Zaldivar-Lopez S, et al. Epsilon aminocaproic acid for the prevention of delayed postoperative bleeding in retired racing greyhounds undergoing gonadectomy. Vet Surg 2012; 41:594–603.
21. Henry DA, Carless PA, Moxey AJ, et al. Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion. Cochrane Database Syst Rev 2011; 16:CD001886.
22. Shmalberg J, Hill RC, Scott KC. Nutrient and metal analyses of Chinese herbal products marketed for veterinary use. J Anim Physiol Anim Nutr 2011; 97:305–314.
23. Fletcher DJ, Blackstock KJ, Epstein K, et al. Evaluation of tranexamic acid and e-aminocaproic acid concentrations required to inhibit fibrinolysis in plasma of dogs and humans. Am J Vet Res 2014; 75:731–738.