Percutaneous Doxycycline Treatment of Aneurysmal Bone Cysts With Low Recurrence Rate: A Preliminary Report

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Abstract

Background Aneurysmal bone cyst (ABC) has a recurrence rate of between 12% and 71% without en bloc resection or amputation. There is no percutaneous ABC treatment drug regimen demonstrating consistent evidence of bone healing with recurrence of < 12%. Doxycycline has properties that may make it appropriate for percutaneous treatment.

Questions/purposes We therefore asked: (1) Is there reduction in ABC lytic cyst volume with injectable

doxycycline? (2) Is it associated with thickening of involved bony cortex? (3) Is the recurrence rate after percutaneous treatment < 12%?

Methods We retrospectively reviewed 20 patients who underwent percutaneous treatment of ABCs with doxycycline from 2006 to 2010. The mean age was 10 years (range, 3–18 years). There were 21 treatment locations: humerus (six), spine (five), clavicle (two), fibula (one), femur (two), ulna (two), tibia (two), and scapula (one). Twenty patients completed treatment involving 118 treatment sessions (two to 14 sessions per patient). Treatment response was evaluated radiographically by measuring the lytic component and thickness of involved cortex. Recurrence was indicated by new areas of lytic destruction after completion of treatment. The minimum followup was 24 months (mean, 38 months).

Results Twenty of 20 patients demonstrated reduction in lytic destruction and bony healing. All patients demonstrated cortical thickening. One patient demonstrated recurrent minimal lytic destruction after 20 months of observation.

Conclusions In this series, patients undergoing percutaneous doxycycline treatment of ABCs demonstrated a healing response and a recurrence rate of 5% at more than 24 months.

Level of Evidence Level IV, therapeutic study. See Guidelines for Authors for a complete description of levels of evidence.

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Introduction

Aneurysmal bone cyst (ABC) is one of the most aggressive, benign bone tumors and may be difficult to treat

without en bloc resection or amputation [8, 11, 16, 17, 25, 33–35, 42, 44]. The recurrence rate of ABCs after traditional surgical treatments ranges from 12% to 71% (71% in children < 10 years) with 90% detected within 2 years of surgical treatment [11, 16, 17, 25, 28, 35, 42, 44]. Recurrence is particularly associated with juxtaphyseal locations of ABCs in skeletally immature patients [16]. In a large series, treatment with curettage and cryotherapy has a recurrence rate of 5% [33]. As an alternative to surgical treatment, percutaneous treatment of ABCs has been attempted with ethibloc and polidocanol with healing response rates ranging from 58% to 94%; the complications have included pulmonary embolism, skin necrosis, pain, swelling, and fever [1, 36]. Polidocanol is not approved for use in the United States and ethibloc use has been abandoned for ABC because of major complications [41]. To date, no single agent has found widespread use for percutaneous treatment of ABCs.

ABCs demonstrate specific translocational events, most commonly found on chromosomal bands 16q22 and 17p13 with TRE17/ubiquitin carboxyl-terminal hydrolase 6 (USP6) oncogene rearrangements found in primary ABCs [2, 3, 10, 30–32, 38]. Multinucleated giant cells in ABCs express osteolytic features of osteoclasts with high levels of matrix metalloproteinases (MMP-9 and MMP-10), tartrate-resistant acid phosphatase, and cathepsin K [23, 26]. ABCs and osteolytic lesions of bone reportedly express high levels of vascular endothelial growth factor (VEGF) in addition to MMPs [23]. In ABCs, the bony destructive process is largely associated with TRE17/USP6 oncogene promotion and upregulation of MMP production, similar to destructive processes associated with MMP production in bone malignancies [5, 43]. TRE17/USP6 promotion blocks osteoblastic maturation through an autocrine mechanism that involves bone morphogenic protein dysregulation [24].

Doxycycline is an antibiotic that heals microcystic and macrocystic lymphatic malformations that are associated with elevated VEGF and MMPs [6, 29, 39, 40]. In bone and soft tissue malignancy cell cultures, doxycycline demonstrates antitumoral properties with inhibition of MMP and angiogenesis [12, 13, 15], inhibition of osteoclastic function, and induction of osteoclastic apoptosis [12, 13, 15, 19]. Doxycycline enhances osteoblastic healing of bone defects in dogs [8].

We treated a cystic sacral bony lesion as a possible lymphatic malformation with percutaneous doxycycline treatment. As a result of the question on the interpretation of the original core biopsy, the patient underwent subsequent surgical curettage 1 week after percutaneous doxycycline treatment. Histologic sections confirmed a diagnosis of ABC and documented necrosis of the ABC, which we presumed to be associated with the prior doxycycline therapy. After this patient, we treated two

additional patients (two skull lesions) with doxycycline injection 1 to 2 weeks before surgical resection and found further histologic evidence of tumor necrosis. Given the histologic evidence of necrosis after doxycycline injection in three patients with ABC, the question arose as to the potential for doxycycline as an agent for percutaneous treatment of ABCs.

The purpose of this study was to answer three questions regarding percutaneous treatment of ABC with doxycycline: (1) Is there reduction of lytic bony destruction? (2) Is there evidence of cortical thickening? (3) Is the recurrence rate after percutaneous treatment < 12%?

Patients and Methods

We retrospectively reviewed 20 patients with 21 ABC sites who underwent percutaneous treatment with doxycycline (off-label use) delivered in a protein foam delivery system from 2006 to 2010. The indications for doxycycline injection were: (1) recurrence after surgical curettage and bone grafting (n = 6); (2) surgeon request for percutaneous treatment as an alternative to surgical treatment (n = 15); and (3) patient request for percutaneous treatment as an alternative to surgical treatment (includes those treated primarily with doxycycline injection and those requesting no further attempts at surgical intervention [n = 21]). The contraindications for surgery were (1) a history of prior surgery with recurrence (one or more recurrences); and (2) location determined by the surgeon to be inoperable (> 95% of scapula or sacrum). We treated 21 locations: one patient (sites 20/21 in Table 1) presented with scapular and tibial ABCs 31 months apart. The patients ranged from 3 to 18 years of age (mean, 10.3 years) (Table 1). All patients had diagnostic plain radiographs, eight patients had CT scans, and 20 patients had MRI examinations. Eighteen patients had histologic diagnoses of ABCs either from surgical biopsies (n = 5) or core needle biopsies (n = 13) with histologic analysis confirming three diagnostic features of ABC: fibroproliferative stroma, giant cell-like osteoclasts, and vascular spaces. Two patients underwent fine needle aspiration biopsies with cyst fluid and radiographic studies consistent with ABCs. Twenty patient sites had primary ABCs, and one patient site had a secondary ABC in the ulna with fibrous dysplasia. Posttreatment followups ranged from 24 to 63 months (mean, 38 months).

Treatment procedures were performed on an outpatient basis in the interventional radiology suite with general anesthesia or intravenous sedation. Pretreatment consultation (and posttreatment followup visit) included obtaining the patient history by the treating radiologist of pain associated with the ABC (separate from any associated pathologic fracture). ABC percutaneous access, with 14- to

Table 1. Patient data from this aneurysmal bone cyst series

Patient number	Age (years)	Site	Number of treatments	Doxycycline treatment dose range (mg)	Pretreatment lytic volume (mL)	Pretreatment cortical thickness (mm)	Posttreatment lytic volume (mL)	Posttreatment cortical thickness (mm)	Followup (months)
1	17	Cervical spine	5	80–200	8	0.1	1.26	1.9	40
2	19	Cervical spine	5	50–384	57	< 0.1	0.4	2	30
3	10	Thoracic spine	3	63–100	31	< 0.1	0.1	2.8	63
4	7	Fibula	14	50–200	2	0.1	0.01 mL	3.1	26
5	5	Femur-proximal	2	280–360	18	< 0.1	0.2	3	39
6	16	Femur-distal	4	160–280	71	< 0.1	8.4	2.8	28
7	7	Clavicle	4	15–190	6	< 0.1	0.001	3	44
8	12	Clavicle	5	200–400	45	< 0.1	1.3	3	42
9	6	Humerus	2	80–100	38	0.5	0.17	4.3	48
10	8	Humerus	3	80–400	48	1	No lytic areas	8	30
11	16	Humerus	4	205–800	111	0.5	0.98	6.4	41
12	11	Humerus	10	120–600	67	0.5	0.03	6.3	36
13	4	Humerus	10	40–500	39	< 0.1	0.01	4.2	28
14	6	Humerus	2	200 (twice)	10.0	0.9	0.4	3.7	47
15	14	Humerus	4	400–760	23	0.9	0.03	4.1	32
16	17	Sacrum	10	160–1200	1404	0.1	233	6.0	24
17	18	Sacrum	10	300–1000	340	0.1	44	7	40
18	16	Ulna	5	50–240	13	1.0	0.3	3.5	36
19	3	Ulna	6	5–130	6	0.2	No lytic areas	2.7	48
20	8	Scapula	5	100–240	108	< 0.1	0.014	4.0	58
21	11	Tibia	5	120–400	20	0.1	0.15	2.5	28

25-gauge needles, was performed with sonographic, fluoroscopic, or CT guidance. Needle size was based on the thickness (or absence) of cortical bone overlying the ABC and on the need for access for a core biopsy. Small-gauge (20- to 25-gauge) needles were used for direct intraparenchymal tumor injections of doxycycline with the absence of bony cortex, which allowed access. Sonography was used for access when there was either an absence of overlying bone or a very thin cortical bone demarcating the expansile ABC. Contrast cystograms with fluoroscopy or CT were performed before the doxycycline injection. When contrast cystograms demonstrated considerable draining veins, a tourniquet was applied to the extremity to maintain intraosseous drug delivery and decrease the potential for pulmonary embolism of doxycycline. Doxycycline (10 mg/mL) was used as the chemical ablation agent and delivered as a protein foam (a mixture of doxycycline and 25% albumin and agitated with air to create a stable protein foam delivery system). The hospital pharmacy prepared 200 mg doxycycline in 5 mL of diluent (40 mg/mL doxycycline). Five milliliters of 25% human serum albumin (Talecris Biotherapeutics, Research Triangle Park, NC, USA) was added to the doxycycline liquid in the interventional radiology suite (thus 20 mg/mL doxycycline in the albumin mixture). Five milliliters of the

doxycycline/albumin mixture was mixed with 5 mL air agitated 30 times between two 5-mL syringes with an interposed stopcock to make a 10-mg/mL doxycycline foam concentration for injection. Doxycycline was injected into the cystic locules and, when possible, into the solid elements of the ABC (sonography was used for guidance during direct injection into solid ABC elements). Injection into cystic spaces was performed in 12 of the 21 lesions with at least two needles to allow for cyst decompression at the end of the injection sequence and reduce risks of skin burn and doxycycline-induced nerve injury [20–22]. Multilocular ABCs required one or two needles in each locule (up to 14 needles in a massive sacral ABC). Treatment of lesions with pathologic fractures was delayed at least 6 weeks until partial fracture healing was radiographically documented. Fracture healing and respective immobilization and physiotherapy were prescribed and monitored by the orthopaedic surgeon responsible for treating the fracture. Postprocedural pain was managed with either oral nonsteroidal, antiinflammatory agents or oral narcotic analgesics.

Once the patient was pain-free and pathologic fracture healing was documented, upper extremity lesions were not immobilized. Patients with lower extremity ABCs were assessed (by JLM) for lower extremity immobilization with

appropriate immobilization prescription. All patients were restricted from recreational or work activities that placed the ABC location at risk for fracture. Followup radiographs or CT studies were routinely performed at 6 weeks after the first treatment and at 10 weeks after subsequent treatments; subsequent treatment procedures were scheduled 8 weeks after the first treatment and at 12-week intervals thereafter (evaluation after the first treatment in these initial 20 patients was performed at 6 weeks, with treatment 2 weeks later, as a conservative approach to confirm early treatment response with early new bone healing). Treatment was considered completed when either lytic areas were healed with new bone or small lytic areas remained stable after two consecutive treatments. Patients were informed of a minimum 5-year surveillance period after treatment to identify lucent foci that expand and demonstrate the need for further treatment. New areas of bony lysis (or expansion of lucent foci) during the surveillance period are regarded as recurrence and were treated with further percutaneous doxycycline injections (two foci, one patient) under CT guidance.

When treatment was completed, followup radiographs were performed every 6 months for 12 months and annually thereafter for 5 years (the minimum surveillance period was 2 years for inclusion in this study). Routine radiographic (or CT) imaging was performed with images reviewed by two radiologists (WES, BA who was not associated with the treatment). Images were evaluated for (1) volume reduction of the lytic, destructive ABC lesions comparing cyst volume at last followup with pretreatment volume (volume calculations use the formula for a typical ellipsoid [14]); (2) bony healing of the ABC assessed by thickening of involved bony cortex comparing that at pretreatment with last followup; thickness was measured at the point of greatest cortical thinning before treatment and the same point after treatment, from the outer periosteal surface to the endosteal cortical surface (of the single cortical surface adjacent to the ABC); and (3) evidence of recurrent bony osteolysis or an expansion during the followup surveillance. Cyst volume and cortical thickness measurements (measurements represent the average of three measurements at the same point) were performed by a single radiologist (WES).

All 20 patients (21 locations) completed full protocol treatment that involved 118 treatment sessions (two to 14 sessions per patient; mean, five sessions) (Table 1). Patients requiring more than eight procedures had either two massive (> 10 cm) sacral lesions (Fig. 1) or a fibular ABC that recurred after three attempts at surgical curettage and bone graft placement. Sixteen patients reported pain in the affected location before treatment (four patients with pathologic fracture of the humerus reported no pain before fracture). All 16 patients reported they were pain-free within 3 days after the first therapeutic procedures.

We determined differences (measurement of lytic focus volume) in bony lytic regions before and after treatment by both the Shapiro-Wilk normality test and the one-sample t-test. We determined differences in bone healing, specifically thickness of affected bony cortex, before and after treatment, by both the Shapiro-Wilk normality test and paired t-test. Any patient with recurrent areas of expansile osteolysis was treated with further percutaneous doxycycline treatment.

Results

We observed a lesion volume reduction ($p < 0.001$) of the ABC lytic foci in all 20 patient sites (Table 2). Volume

Fig. 1A–B Recurrence of a 16-cm sacral and bilateral iliac ABC after surgical resection in a 17-year-old girl is shown. **(A)** This sagittal T2-weighted MR image demonstrates the 16-cm sacral ABC after surgical resection and before percutaneous treatment. **(B)** This 3-year followup CT scan reconstruction of a coronal demonstrates dense bony healing of the sacral ABC after 11 treatment sessions with doxycycline ablation targeting individual locules. The patient was asymptomatic after treatment without gait or nerve dysfunction.

reduction was noted after two treatments in 19 patient sites (90%). In the remaining two patient sites, ABC lytic reduction was noted after the third treatment. Lytic component volume reduction was evaluated discretely and separately from evidence of new bone healing. Two patients (distal ulna and distal clavicle) showed complete disappearance of lytic destructive foci with normalization of the associated marrow.

Eighteen of 21 sites undergoing treatment demonstrated decreased ($p < 0.001$) lytic volume and thickening ($p < 0.001$) of the affected cortex (Fig. 2). Eight of these 21 sites in patients older than 13 years of age healed with residual bulbous deformities (Figs. 1–3).

One patient had a 1-cm focus of recurrence detected 20 months after cessation of treatment; this area was treated with doxycycline injection with resolution. The six patients treated for recurrence after surgical curettage and bone graft placement responded with healing without subsequent recurrence during the followup periods.

One complication occurred: one patient had focal (1 cm) skin necrosis resulting from doxycycline cyst overpressurization with extravasation before routine use of secondary decompression needles in large cysts. No complications of nerve injury, infection, or vascular thrombosis occurred. No patient had further pathologic fracture after initiation of percutaneous doxycycline therapy. No patient required physical therapy rehabilitation to return to full activity and normal function of the affected site. One patient had two metachronous ABCs: one in the scapula (nonsurgical candidate) and a second in the proximal tibia presenting 31 months apart. In this patient, both the scapular and tibial ABCs responded to percutaneous therapy with excellent healing and bony remodeling.

Discussion

ABC is considered a mesenchymal neoplasm [10, 30–32] characterized by spindle cell proliferation with *TRE17/USP6* as the major oncogene [10, 30–32]. The translocational event on chromosomal bands 16q22 and 17p13, with *TRE17/USP6* oncogene rearrangement, is found in 69% of primary ABCs [10, 30–32]. The pathogenesis of the ABC is now believed to be a novel oncogenic mechanism with *TRE17/USP6* transcription associated with upregulation of VEGF and MMP production, increased osteoclastic activity, and *TRE17/USP6* promotion that blocks osteoblastic maturation through an autocrine mechanism involving bone morphogenic protein dysregulation [5, 24, 43]. MMP is a potent collagenase secreted by bony neoplasms that contribute to collagen destruction, angiogenesis (along with VEGF), and osteoclastogenesis. Given this described understanding of ABC as a clonal neoplasm with destructive fibroblastic stromal component and giant cell-like osteoclasts, and oncogenic upregulation of MMPs and VEGF, the rationale for ABC treatment with doxycycline is consistent with the stromal necrotic effects and cellular-level inhibitory effects of doxycycline described in the introduction. The purpose of this study was to answer three questions regarding percutaneous treatment of ABC as a clonal neoplasm with targeted doxycycline injection: (1) Is there reduction of lytic bony destruction? (2) Is there evidence of cortical thickening? (3) Is the recurrence rate after percutaneous treatment $< 12\%$?

Limitations of the study include the following. First, this series includes a relatively small number of patients. As a preliminary series, 20 patients provides evidence for further study of this treatment regimen. Second, our followup ranged from 24 to 63 months. Given the median recurrence

Table 2. Results of published aneurysmal bone cyst treatment series compared with the current study

Study	Publication year	Number of patients	Therapeutic procedure	Recurrence rate	Minimum followup (months)
Current study	2013	20	Percutaneous injection—doxycycline	5%	24
Mankin et al. [28]	2005	150	Curettage with graft or methacrylate	20%	72
Freiberg et al. [16]	1994	7 (≤ 10 years)	Curettage, graft	71%	24
Dormans et al. [11]	2004	45	Curettage, graft	18%	24
Gibbs et al. [17]	1999	40	High-speed burr curettage, graft	12%	87
Peeters et al. [33]	2009	80	Curettage, cryotherapy	5%	24
Rastogi et al. [36]	2006	72	Sclerotherapy—polidocanol	15%	34
Adamsbaum et al. [1]	2003	17	Sclerotherapy—alcohol solution of zein	18%	12
Vergel De Dios et al. [42]	1992	16	Wide excision	0%	24
Zenonos et al. [44]	2012	14 (spine)	Resection	14%	56

Fig. 2A–E Images from a 3-year-old girl with distal left ulna ABC and fibrous dysplasia are shown. **(A)** This frontal radiograph of the distal ulna shows the expansile ABC (straight arrow) and adjacent area of fibrous dysplasia (curved arrow). **(B)** A fluoroscopic spot view documents surgical curettage and bone graft placement. **(C)** A radiograph obtained 3 months after curettage and grafting demonstrates the recurrent ABC with graft resorption and tumor progression

(arrow). **(D)** A spot radiograph during percutaneous ABC treatment demonstrates contrast definition of the cystic component of the ABC. **(E)** A 4-year followup radiograph of the wrist demonstrates healing and dimetaphyseal concavity of the treated ulna (straight arrow), including evidence of healing and reduction in the fibrous dysplastic component (curved arrow).

rates for this lesion ranging from 18 to 24 months [8, 17, 34], this followup (mean, 38 months) should capture more than 90% of potential recurrences [8, 17, 28, 34, 35]. These patients require and will continue further in 5-year surveillance to determine whether their ABCs will ultimately recur. Third, the histologic diagnosis in the majority of patients was made with limited tissue sampling, potentially missing a more aggressive primary lesion. In this series, no patient presented with delayed diagnosis of aggressive or malignant neoplasm. Fourth, interobserver variation of the radiographic measures was not evaluated in this study and we cannot comment on their reliability. Further studies are planned to formally evaluate interobserver measurement variation and more detailed description of radiographic

changes during ABC healing after doxycycline injection treatments. Lastly, this study represents a single cohort study. Further studies on percutaneous treatment of ABC may include multiple arms including supplemental use of oral doxycycline or primary treatment of ABC with RANK-ligand inhibitors such as denosumab [9] as well as more rigorous evaluation of interobserver measurement variations of cyst/lesion volume and cortical thickness.

We found all patients had a reduction in the size of the area of lytic destruction if not complete resolution of lytic foci (in two patients). This consistent response compares favorably with treatments including en bloc resection and amputation [35, 42, 44]. Furthermore, the lack of need for posttreatment physical rehabilitation (once pathologic

Fig. 3A–C Images from an 11-year-old boy with left tibial ABC (metachronous ABCs [right scapula, left tibia] presenting 31 months apart) are shown with percutaneous treatment. **(A)** A frontal radiograph of the left knee demonstrates the proximal tibial metaphyseal juxtaphyseal ABC (arrows). **(B)** A fluoroscopic image treatment of the ABC demonstrates contrast material outlining the

ABC cysts. **(C)** A 3-year followup radiograph of the left knee demonstrates healing of the ABC, proximal metaphyseal remodeling, and preservation of tibial physeal growth function with distal migration of the bone scar away from the original juxtaphyseal location (arrows).

fractures heal) offers patients greater mobility and maintenance of normal activities of daily living (recreational and work activity within limits set by the patient's orthopaedic surgeon) during the therapeutic regimen. Although the exact mechanism of regression is not known, pathology results in three patients not completing the full protocol of percutaneous treatment suggest direct cytotoxic action on the mesenchymal tumoral ABC component in addition to known metabolic therapeutic targets of doxycycline that inhibit VEGF, MMP, and osteoclast function [4, 5, 7, 12, 13, 15, 18, 19, 24, 27, 43].

An increase in cortical thickness, reduction in lytic volume, and conversion of outward convex metaphyses to inward concavity after percutaneous doxycycline treatment suggest ABCs respond to stimulation with doxycycline (complementing normal bone healing factors). In addition, evidence of new bone healing provides key information for the physicians involved that treatment was progressing in the proper direction. Evidence of healing in 100% of patients compares favorably with surgical and nonsurgical care series [1, 11, 16, 17, 25, 28, 33, 35, 36, 42, 44].

The 5% recurrence rate demonstrated in this series, particularly with juxtaphyseal lesions, provides an acceptable comparative recurrence rate [1, 11, 16, 17, 25, 28, 33, 35, 36, 42, 44] with which to pursue further study of this percutaneous treatment option. Furthermore, when recurrence (evidence of residual foci of tumor cells) occurs, patients are able to pursue a minimally invasive option of percutaneous treatment of small recurrent foci.

The consistent response of ABCs to doxycycline in this series with cyst resolution and bony healing is compatible with the multiple therapeutic actions of doxycycline in bony pathology. In addition to a radiographic demonstration of tumor involution and bony healing, a pathologic analysis of three operative tissue specimens at the authors' institution, after percutaneous doxycycline treatment, documented the direct cytotoxic effect of doxycycline on the mesenchymal ABC cells. Beyond simple cytotoxicity, doxycycline is antiangiogenic [18, 37], a potent inhibitor of MMP [12, 13, 27], an inhibitor of osteoclastic activity [12, 13], induces apoptosis in osteoclasts, and promotes osteoblastic activity [4, 7, 12, 13, 15, 19]. These multiple sites of action serve well to target the neoplastic cell of an ABC, destructive osteoclasts, tumor vascularity ingrowth, and support osteoblastic healing after tumor ablation.

The protein foam doxycycline delivery system serves multiple purposes. Protein foam is highly echogenic, allowing precise sonographically guided drug delivery into both noncommunicating cysts and solid tumor nodules. Sonographically guided injection is targeted early in therapy before bony healing that will obscure sonographic visualization of the cyst and neoplastic cell masses lining or adjacent to cysts. Additionally, given the demonstrated potential for skin necrosis and literature reports of nerve damage from excessive doxycycline administration [20–22], precise drug delivery is critical in both cysts and solid ABC components. The protein foam is viscous and maintained in the cysts after injection (postprocedural CT

performed in one patient demonstrated the foam persisting for 3 days after injection).

In conclusion, our observations provide initial evidence of healing response of ABCs to doxycycline therapy, including recurrent ABCs after surgical treatment and after primary percutaneous treatment. Doxycycline is a multifactorial agent with demonstrated inhibition of MMP production, osteoclastic function, and angiogenesis as well as induction of apoptosis of osteoclasts, direct ABC mesenchymal cell cytotoxicity, and promotion of osteoblastic healing. Doxycycline, as an osteotropic agent in the percutaneous treatment of ABC, results in reduction of the ABC lytic component, new bone healing, and a low recurrence rate. Furthermore, percutaneous delivery of doxycycline offers patients a minimally invasive option for treatment of localized recurrence. As a result of the healing responses as measured in this study and low rate of recurrence of ABC with doxycycline injection, this is now the authors' preferred method of treatment of ABC. Independent confirmation of these results will be important for future expansion of ABC treatment recommendations.

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