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Percutaneous Cutibacterium acnes Inoculation in Sheep IVDs: Safe Delivery and Variable Bacterial Clearance at 1–6 Months

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ABSTRACT

The anaerobic microorganism Cutibacterium acnes has been increasingly associated with the onset and progression of degenerative disc disease (DDD), though a direct causal link has yet to be confirmed. To clarify the potential pathogenic role of this bacterium, animal models that more accurately reflect human intervertebral disc (IVD) anatomy, physiology, and biomechanics are needed. In this proof-of-concept experiment, we aimed to demonstrate for the first time that C. acnes can be percutaneously injected into sheep IVDs under controlled conditions. Following our established protocol, two sheep received inoculations with a C. acnes strain (8.3×10^6 CFU/disc) originally isolated from a human degenerated disc. No adverse clinical signs were detected. After one month, all three infected discs from the first animal yielded C. acnes growth, although at a reduced bacterial burden (5.12×10^4 to 6.67×10^4 CFU/disc). At six months, cultures from the second animal were negative, suggesting bacterial clearance. These findings confirm that safe, image-guided percutaneous inoculation of C. acnes into ovine IVDs is feasible. Future studies using this model should focus on evaluating whether C. acnes contributes to disc degeneration or associated pathological alterations.

Keywords: Cutibacterium acnes, Ovine model, Intervertebral disc, Percutaneous injection, Bacterial infection

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Introduction

The 2017 Global Burden of Disease report identified low back pain (LBP) as the foremost cause of disability worldwide [1]. In the United States, approximately 80% of individuals are expected to experience LBP during their lifetime—a figure projected to rise with aging populations and risk factors such as sedentary behavior and obesity [2]. Although multiple factors contribute to LBP, degeneration of the intervertebral disc (IVD) is strongly implicated [3]. There is currently no curative treatment for degenerative disc disease (DDD), largely because its underlying mechanisms—including nutritional deficiencies, inflammatory mediators, biomechanical stress, and genetic susceptibility—are incompletely understood.

Over the past two decades, a growing body of evidence has suggested that microbial infection, particularly by the anaerobic bacterium Cutibacterium acnes (formerly Propionibacterium acnes), could play a role in the pathogenesis of DDD and discogenic pain [4–14]. C. acnes is a common commensal organism of human skin and is best known for its involvement in acne vulgaris [15]. Beyond dermatologic disease, it is also implicated in osteomyelitis, ocular and dental infections, prosthetic device–related infections, and has been linked to conditions such as prostate disorders and sarcoidosis [16–22]. Within degenerated human discs, C. acnes has been detected in a biofilm-like arrangement, indicating that its presence is unlikely due to surgical contamination [23, 24]. Discs colonized by C. acnes often exhibit type I Modic changes (MCs) in vertebral endplates on MRI scans [25–27]. In

animal models, infection of rabbit discs with C. acnes has been shown to induce endplate inflammation and degenerative alterations consistent with MCs [28, 29]. Despite these findings, the bacterium's etiological contribution to DDD remains debated, emphasizing the need for further in vivo research using physiologically relevant models. Accurate animal models would not only clarify causal mechanisms but also support preclinical testing of new therapeutic approaches [30].

A variety of animal species—such as rabbits, dogs, and sheep, as well as rat and bovine caudal discs—have been employed in IVD research. However, several of these models (e.g., rats, pigs, rabbits, and cattle) exhibit limitations because their lumbar discs differ from those of humans in cellular composition, dimensions, and biomechanical loading [31]. Many animals, including rats, pigs, cats, rabbits, and some dogs, retain notochordal cells into adulthood, which aid disc maintenance [32]. By contrast, humans and certain canine breeds lose these cells after birth, leading to a higher predisposition to spontaneous DDD [32].

Sheep, however, share notable similarities with humans in disc size, mechanical environment, and the early postnatal loss of notochordal cells [30–34]. They also recover effectively from surgical interventions and can be maintained long term, making them ideal for chronic experimental studies [30]. Consequently, sheep have been extensively used for DDD modeling, device testing, and cell-based therapeutic research [30]. Moreover, the use of larger animals minimizes scaling discrepancies when translating findings to human clinical trials [34].

Given these anatomical and physiological advantages, establishing a sheep model for C. acnes IVD infection would be invaluable for exploring its pathogenic potential in disc degeneration. Therefore, this study aimed to provide the first experimental evidence that C. acnes can be introduced safely and effectively into sheep intervertebral discs via percutaneous inoculation, allowing for both acute and chronic infection modeling.

Materials and Methods

Animals

Two adult Dorset cross ewes, approximately 2.5 years old and weighing around 60 kg, were selected for the trial. Each animal was permanently marked with a USDA identification tag to eliminate mix-ups (#1283 and #1286). They were kept separately in 5 × 5 ft pens, fed grass hay twice daily, and received no additional supplements. All animal handling procedures followed Purdue University IACUC approval and complied with established animal welfare guidelines.

Anesthesia

A uniform sedation and anesthetic plan was followed for MRI imaging and disc injection. Sheep were pre-sedated with xylazine (AnaSed; Akorn, IL, USA; 0.03 mg/kg IV) and butorphanol (Torbugesic; Zoetis, MI, USA; 0.01 mg/kg IV). Induction was achieved with ketamine (VetaKet; Akorn; 2.2 mg/kg IV) and diazepam (Hospira; IL, USA; 0.06 mg/kg IV). To ease intubation, a few drops of 2% lidocaine (AnaSed; Akorn) were applied to the vocal folds. Anesthesia maintenance used isoflurane, and each animal received lactated Ringer's solution (10 mL/kg/hr) during the procedure. For postoperative analgesia, buprenorphine (Par Pharmaceutical, NY, USA; 0.005 mg/kg IV) and flunixin meglumine (Merck & Co., NJ, USA; 1.1 mg/kg IM) were administered.

MRI

All imaging was conducted using a 1.5 Tesla GE Signa LX scanner (General Electric, Milwaukee, WI, USA) with animals positioned in dorsal recumbency. Scans were independently reviewed by three board-certified radiologists. A baseline MRI was obtained under general anesthesia before performing targeted intradiscal injections by a certified neuroradiologist (BH). Subsequent monthly MRIs were carried out under the same anesthetic conditions. Due to severe cold weather, scans were omitted at months 3 and 5 for sheep #1286.

Bacterial injectate

The inoculum used was Cutibacterium acnes type IA1 (subsp. acnes) strain PD271, originally isolated from a human degenerated disc and supplied by the Central European Institute of Technology (Brno, Czech Republic; OS). Cultivation took place anaerobically in brain heart infusion broth at 37 °C until the logarithmic phase. After harvesting, bacterial pellets were washed and re-suspended in phosphate-buffered saline (PBS) (Fisher Scientific, Waltham, MA, USA). Colony counts were confirmed using modified Clostridial Reinforced Agar (CRA) (Becton,

Dickinson and Co., Cockeysville, MD, USA). Each disc received ~0.1 mL of suspension containing approximately 8×10^7 CFU/mL, matching bacterial loads used in previous rabbit infection models [28, 29].

Injection protocol

The injection method, derived from earlier rabbit studies [28, 29, 35], was first practiced on an unrelated sheep using Omnipaque 180 Iohexol contrast medium (GE Healthcare/McKesson, MA, USA) to verify needle positioning by computed tomography (GE VCT 64 slice, General Electric).

Animals were anesthetized, and the lumbar region was clipped, cleaned with chlorhexidine, and covered with sterile drapes. While in prone position, five 6-inch 25/20-gauge Quincke coaxial spinal needles (#183109; Halyard Health, Alpharetta, GA, USA) were guided into selected discs using fluoroscopy (GE OEC 9900 Elite, GE OEC Medical Systems, UT, USA). The 20-gauge introducer was inserted about 5.5 cm from the midline at a 30° medial angle, ending at the outer annulus fibrosus. A 25-gauge needle was advanced through the introducer to the nucleus pulposus. A 1 mL Hamilton Gastight syringe (#81301; Hamilton Company, Reno, NV, USA) held the anaerobically maintained inoculum. Discs L2–3, L4–5, and L6–7 were injected with C. acnes, L3–4 served as the needle-only control, and L5–6 received 0.12 mL of sterile saline.

Euthanasia and post-mortem procedures

Euthanasia followed AVMA 2020 guidelines [36], performed with sodium pentobarbital (Euthanasia Solution, MWI, ID, USA, or Euthasol, Virbac AH, TX, USA; 390 mg/mL, 15 mL IV). To evaluate short-term infection, sheep #1283 was euthanized 1 month post-inoculation; sheep #1286 was euthanized at 6 months to assess persistence or clearance. Immediately following euthanasia, the lumbar spine was dissected, soft tissues were removed, and discs were aseptically extracted in full.

Disc tissue sampling

Recovered discs were homogenized in sterile PBS under anaerobic conditions using an Omni Tissue Homogenizer (Omni International, Kennesaw, GA, USA). Serial dilutions were prepared in PBS, and 4 µL from each dilution was plated on CRA agar for anaerobic incubation at 37 °C over an extended period for enumeration. Additionally, Gram staining was performed on samples from sheep #1286 after 6 months.

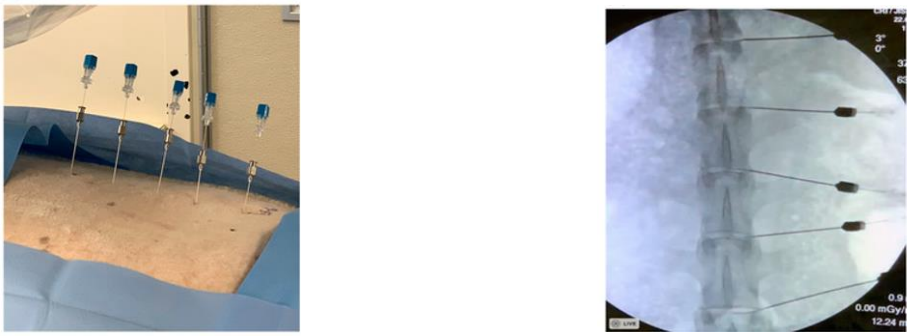
Statistical analysis

Data analysis employed the Wilcoxon matched-pairs signed-rank test (two-tailed) for evaluating differences between groups.

Results and Discussion

Fluoroscopically guided Percutaneous delivery of C. acnes *into sheep IVDs*

Using fluoroscopic imaging, six-inch 25/20-gauge coaxial spinal needles were precisely advanced percutaneously into the nucleus pulposus of the sheep lumbar intervertebral discs prior to Hamilton syringe-mediated inoculation with *C. acnes* **(Figure 1)**. When performed by an experienced neuroradiologist, the procedure was technically straightforward and clearly visualized under biplanar C-arm fluoroscopy **(Figure 1b)**.



a) b)

Figure 1. a) 25-gauge needles positioned within 20-gauge introducer needles, sequentially placed in lumbar discs. b) Fluoroscopic AP image confirming correct needle alignment.

Animal health and welfare

Neither animal exhibited adverse responses following intradiscal administration, and general anesthesia as well as MRI examinations were completed without incident. Both sheep resumed normal activity and feeding shortly after recovery, with no evidence of restricted movement. In the sheep euthanized at one month post-inoculation (USDA#1283), a "softening" sensation was noted during injection into the L5–6 disc that received sterile saline, likely indicating a minor acute annular fissure.

Detection of early C. acnes *colonization*

The animal terminated at one month (USDA#1283) exhibited *C. acnes* growth from all three treated discs following CRA agar culture. The recovered bacterial counts (5.12×10^4–6.67×10^4 CFU per disc) were below the initial inoculum (8×10^6 CFU per disc), but the difference was not statistically significant **(Figure 2).**

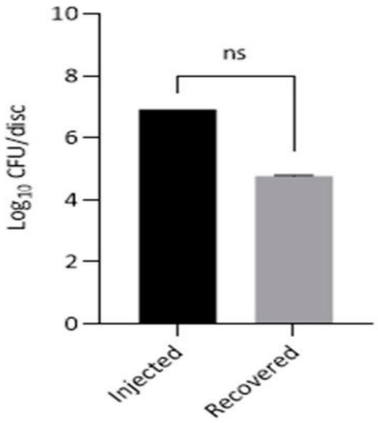
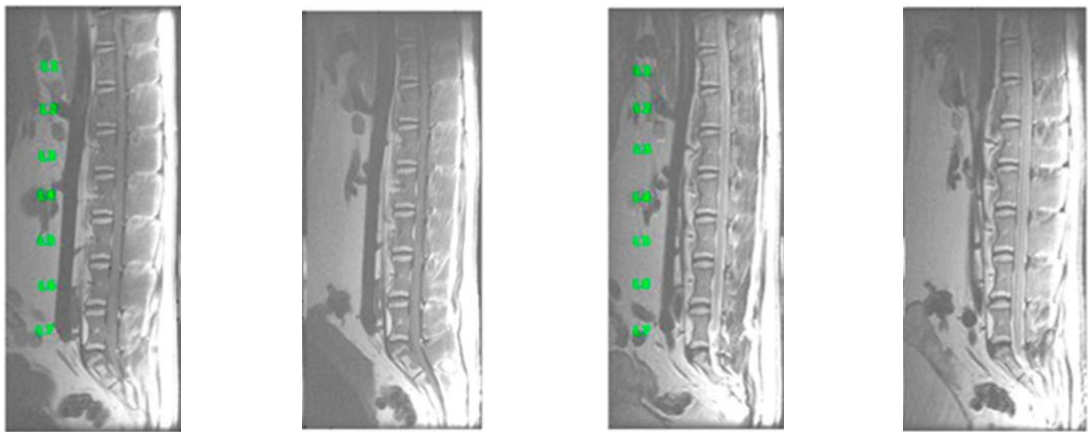


Figure 2. Growth of *C. acnes* colonies from the three lumbar discs of sheep USDA#1283, four weeks post-inoculation. Data represent mean ± SEM (log_{10} CFU/disc). Statistical tests were conducted on paired observations.

In contrast, in the second animal euthanized six months post-inoculation (USDA#1286)**,** *C. acnes* was undetectable in all treated discs using aerobic/anaerobic cultures and Gram staining. For both subjects, discs injected with saline or subjected only to needle puncture remained culture-negative**.**

MRI

MRI performed one month after inoculation for the first animal revealed no radiographic differences relative to baseline **(Figure 3)**.



a) b) c) d)

Figure 3. MRI scans of sheep USDA#1283: (a) baseline T1-weighted, (b) 1-month T1-weighted, (c) baseline T2-weighted FS, and (d) 1-month T2-weighted FS images.

Similarly, the six-month MRI series from the second sheep (USDA#1286) demonstrated no detectable alterations in either disc morphology or adjacent vertebral structures at 1, 2, 4, and 6 months post-injection (data not shown).

Discussion

This preliminary investigation aimed to determine the safety and practicality of introducing *C. acnes* directly into ovine lumbar intervertebral discs via a percutaneous approach. The results confirmed the method's feasibility and absence of adverse clinical effects. Given that this was a pilot trial involving large animal models, only two sheep were utilized—each representing a single endpoint—to comply with ethical principles and minimize animal use, consistent with the 3Rs framework (Replacement, Reduction, Refinement). Although this limits the dataset to one biological subject per time point, inoculating three discs per animal provided triplicate technical observations, balancing ethical considerations with experimental reproducibility.

Our technique for reaching the nucleus pulposus aligns with the observations of Elliott *et al*. [37], who reported minimal annular disruption when needle diameter/disc height ratios remained below 40%, with negligible yet nonsignificant effects between 25–40%. The 25-gauge needle employed here offered sufficient rigidity to traverse skin, fascia, and muscle while maintaining disc integrity. In Elliott's ovine model, 27-gauge needles caused no discernible damage; although 25-gauge needles were not directly assessed, their 0.455 mm diameter relative to a mean disc height of 3.93 mm yields a ratio of approximately 12% (0.455/3.93)—well below the 40% threshold. Therefore, we anticipated negligible mechanical harm, which was corroborated by our MRI scans showing no post-puncture abnormalities.

For future studies, the 25-gauge system appears optimal—being flexible yet sufficiently firm to penetrate the annulus fibrosus of sheep with minimal structural disruption.

Persistence of C. acnes within Ovine IVDs

Beyond confirming that C. acnes could be effectively delivered into sheep intervertebral discs without inducing major tissue damage, our findings also indicated that the organism remained viable within the disc matrix for at least one month, though with a reduction in bacterial count over this period. By the six-month evaluation point, no viable bacteria were detected through culture or Gram staining, suggesting that C. acnes had been eliminated from the disc tissue.

While false-negative cultures may sometimes occur due to inadequate homogenization of tissue containing intracellular or biofilm-embedded bacteria, this is unlikely here, since all samples were thoroughly homogenized before plating. The lack of detectable bacteria at six months may instead reflect the limited sample size, as only one animal was analyzed at that stage. It remains plausible that other subjects—or exposure to a different C. acnes strain—could produce divergent outcomes.

Earlier studies employing C. acnes in rabbit and rat disc models across extended periods did not assess bacterial persistence following initial inoculation [28, 29, 38], making it uncertain whether the bacteria survived through the experiment's end. Based on our observations and these prior reports, it is conceivable that degenerative disc disease (DDD) in humans may arise from recurrent infection cycles, alternating between clearance and reinfection in structurally compromised discs, or that a transient infection might trigger a sustained inflammatory cascade even after bacterial disappearance.

Supporting this hypothesis, a murine model of C. acnes–induced prostatitis demonstrated bacterial presence in the dorsal prostate at weeks 1 and 2, but no detectable organisms by week 8, despite persistent chronic inflammation on histologic examination [39]. Similarly, a rat model of prostatic infection revealed a progressive decline in C. acnes counts over time, reaching minimal levels at six months [40]. These prior small-animal findings, though in a different organ system, are consistent with the decline in bacterial numbers observed in our six-month ovine samples.

Future investigations would benefit from shorter, sequential sampling intervals—for instance, monthly assessments—to monitor bacterial dynamics, tissue response, and potential development of biofilm or inflammatory remodeling.

Conclusion

This proof-of-concept investigation confirms that sheep lumbar discs can be safely inoculated with C. acnes for in vivo experimental modeling. Subsequent studies employing larger animal cohorts and expanded analytical

endpoints are now necessary to better define the replication pattern, persistence, and pathogenic mechanisms of C. acnes within the ovine intervertebral environment. Establishing this model will enable detailed evaluation of the microbial contribution to disc degeneration and facilitate preclinical testing of antibiotic regimens and novel therapeutic strategies relevant to human DDD.

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