Review Article

Cutibacterium acnes in Spine Pathology: Pathophysiology, Diagnosis, and Management

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Abstract

Cutibacterium acnes, long thought to be skin flora of pathological insignificance, has seen a surge in interest for its role in spine pathology. *C acnes* has been identified as a pathogen in native spine infection and osteomyelitis, which has implications in the management compared with more commonly recognized pathogens. In addition, It has also been recognized as a pathogen in postoperative and implant-associated infections. Some evidence exists pointing to *C acnes* as an unrecognized source of otherwise aseptic pseudarthrosis. Recently, it is hypothesized that low virulent organisms, in particular *C acnes*, may play a role in degenerative disk disease and the development of Modic end plate changes found in MRI. To this end, controversial implications exist in terms of the use of antibiotics to treat certain patients in the setting of degenerative disk disease. *C acnes* continues to remain an expanding area of interest in spine pathology, with important implications for the treating spine surgeon.

Cutibacterium acnes, long thought to be skin flora of pathological insignificance, has seen a surge in interest for its role in human disease. Studies have linked *C acnes* to systemic diseases, such as sarcoidosis, and organ-specific diseases, such as benign prostatic hypertrophy.[1] *C acnes* has garnered attention in orthopaedic surgery because of its strong, and often problematic, link to periprosthetic joint infection, particularly shoulder arthroplasty.[2] In the realm of spine pathology, *C acnes* has similarly been linked to both native infections and postoperative implant-associated infections. More recently, there has been an increase in interest in recognizing the potential role of *C acnes* and degenerative spinal conditions, particularly disk herniation and degenerative disk disease. The evolving role of *C acnes* in spine pathology has the potential to change the way these conditions are treated. This article reviews the current understanding of the role of *C acnes* in spine pathology, with particular emphasis on the evolving potential role of *C acnes* in degenerative spine conditions.

Microbiology

C acnes is an anaerobic, nonspore forming, Gram-positive rod.[1] Not only does *C acnes* live in the superficial skin but also it is present in high numbers in hair follicles and sebaceous glands deeper in the skin. *C acnes* is concentrated in the back and neck, axilla, and chest wall, possibly explaining its involvement in spine and shoulder pathology. Males tend to have higher concentrations of *C*

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Table 1

Common Spondylodiscitis Secondary to High-virulent Organisms Versus *Cutibacterium acnes* Spondylodiscitis

Factors	Common spondylodiscitis	*Cutibacterium acnes* spondylodiscitis
Back pain	Significant	Mild to moderate, rarely significant
Systemic symptoms	Present	Often absent
ESR/CRP	Significantly elevated	Slightly elevated or normal
History of spine procedure	Not necessary	Almost always
Diagnosis	MRI with contrast sufficient, cultures for antibiotic treatment	MRI can be similar to degenerative changes, require tissue culture
Positive cultures for diagnosis	1	2
Nonsurgical management	Absence of organized abscess or neurologic deficit	Absence of organized abscess or neurologic deficit
Surgical management	Failure of IV treatment, neurologic deficit, organized abscess	Failure of IV treatment, neurologic deficit, organized abscess

CRP = C-reactive protein, ESR = erythrocyte sedimentation rate, IV = intravenous

acnes compared with females.[3] In addition, the location and concentration of *C acnes* can vary based on pH, temperature, moisture, and sebum content of the skin.[4]

Native or Non–implant-associated Infections

Although often considered a low-virulent organism, *C acnes* has been rarely associated with native infectious conditions of the spine. In a series of patients with pyogenic osteomyelitis, Carragee[5] reported low-virulent organism as the primary infectious species in 41 of 111 patients (36.9%). Specifically, *C acnes* was found as the primary infectious agent in 4% of patients. Kowalski et al[6] reported a series of nine patients who were diagnosed with *C acnes* vertebral osteomyelitis via two separate positive culture results. Two of these patients had relapse of their infection at 2.5 and 4 years after the initial treatment.

Diagnosis of native spondylodiscitis and/or osteomyelitis in the absence of spinal implants is often a challenging diagnosis to make (Table 1). Patients may complain of only axial low back pain without systemic signs of infection. Up to 97% of patients diagnosed with discitis have a history of spine surgery or procedure, such as lumbar diskectomy or epidural catheter placement for analgesia, but the history may be in the remote past.[7-10] The average delay between the index procedure and development of spondylodiscitis is 34 months.[11] Unlike spondylodiscitis caused by more familiar microorganism, spondylodiscitis caused by *C acnes* may result in normal or only slightly elevated erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP).[6] Confirmatory diagnosis of spondylodiscitis requires advanced imaging with MRI or bone scan if there are contraindications to MRI. Most importantly, microbiological proof of *C acnes* infection is required. Given the possibility of contaminant, a single positive culture may lead to overtreatment of patients.[6] Thus, the authors suggest initiating treatment of non–implant-associated *C acnes* infection if two or more cultures that have been followed for an appropriate amount of time are positive. In general, cultures for *C acnes* should be grown on both aerobic and anaerobic culture media for a minimum of 13 days to maximize isolation.[12] However, 29.4% of *C acnes* diagnoses would be missed if only anaerobic culture media are followed.[12]

Given the rare nature of native spine infections secondary to *C acnes*, no clear consensus on treatment exists. In the absence of abscess formation or neurologic compromise, a course of antibiotic treatment may be reasonable.[6] However, most patients with organized abscess or neurologic symptoms will require surgical decompression and débridement.[6,11] Whenever possible, placement of hardware in the setting of infection should be avoided because cases of relapsed infection has been associated with hardware placement at the time of débridement.[6] In general, good outcomes can be expected in patients with native *C acnes* infection, given appropriate diagnosis and adequate treatment.[6] In general, patients with native *C acnes* discitis can be treated with 6 weeks of parenteral beta-lactam, such as ceftriaxone.[6]

Implant-associated Infection

Postoperative infection after spine surgery, particularly in the setting of implant placement, can be a devastating complication that leads to

additional surgeries and sometimes poor clinical outcomes. Infection can occur either in the early or in the late postoperative period, based on whether the infection presents before or after 4 weeks postoperatively.[13] Latent postoperative infections are a subset that may present years after the index surgery.[13] Although *Staphylococcus aureus* is the most common organism for implant-associated infection within 1 year after surgery, *C acnes* and other skin flora may be responsible for a significant portion of latent infections.[14,15]

LaGreca et al[14] retrospectively reviewed 112 patients who required surgical débridement for infection after instrumented spinal fusion and found that *C acnes* was the most common microbial species in infections that presented more than 1 year after the index procedure. Farley et al[15] compared 20 patients with surgical site infections after pediatric scoliosis surgery with 50 patients without postoperative infection. They identified skin flora, including *C acnes*, as a major causative of infection and recommended adjustment of perioperative antibiotic regimen to include adequate coverage of these bacteria. Shiono et al[16] conducted a prospective clinical study examining wound contamination during posterior spinal deformity surgery, obtaining cultures from the lamina just after exposure, just after instrumentation placement, and just before closure. They found that wound contamination was the highest just before closure, and the most frequent species cultured was *C acnes*. Their findings showed that wound contamination at the time of surgery is mostly from the patient's skin, and the probability of infection increases as the length of surgical time increased.

Similar to native infections secondary to *C acnes*, implant-associated infections may have an indolent clinical picture. Back pain with a history of spine surgery and hardware placement, even after a long symptom-free period, should prompt suspicion for indolent infection. Level of ESR and CRP may be normal or only slightly elevated, and the absence of elevated inflammatory markers should not rule out infection.[17] Additionally, the surgical incision may not show any signs of erythema or breakdown. Radiographic evidence of "halo" formation around screws, osteolysis, or evidence of pseudarthrosis of the fusion mass may be the only objective sign of infection in the absence of other systemic signs or laboratory signs.

A diagnosis of postoperative implant-associated *C acnes* infection generally requires two positive periprosthetic and hardware cultures. As with native *C acnes* infection, both aerobic and anaerobic culture media should be followed for a minimum of 13 days. Two or more positive cultures should prompt surgical management. Antibiotics alone will likely not cure an infection in the presence of hardware. In a subset of patients who cannot tolerate surgery, suppressive antibiotics may be a reasonable option. Surgical management consists of open exploration of the previous surgical site and fusion mass if applicable, removal of hardware if possible, and extensive débridement.

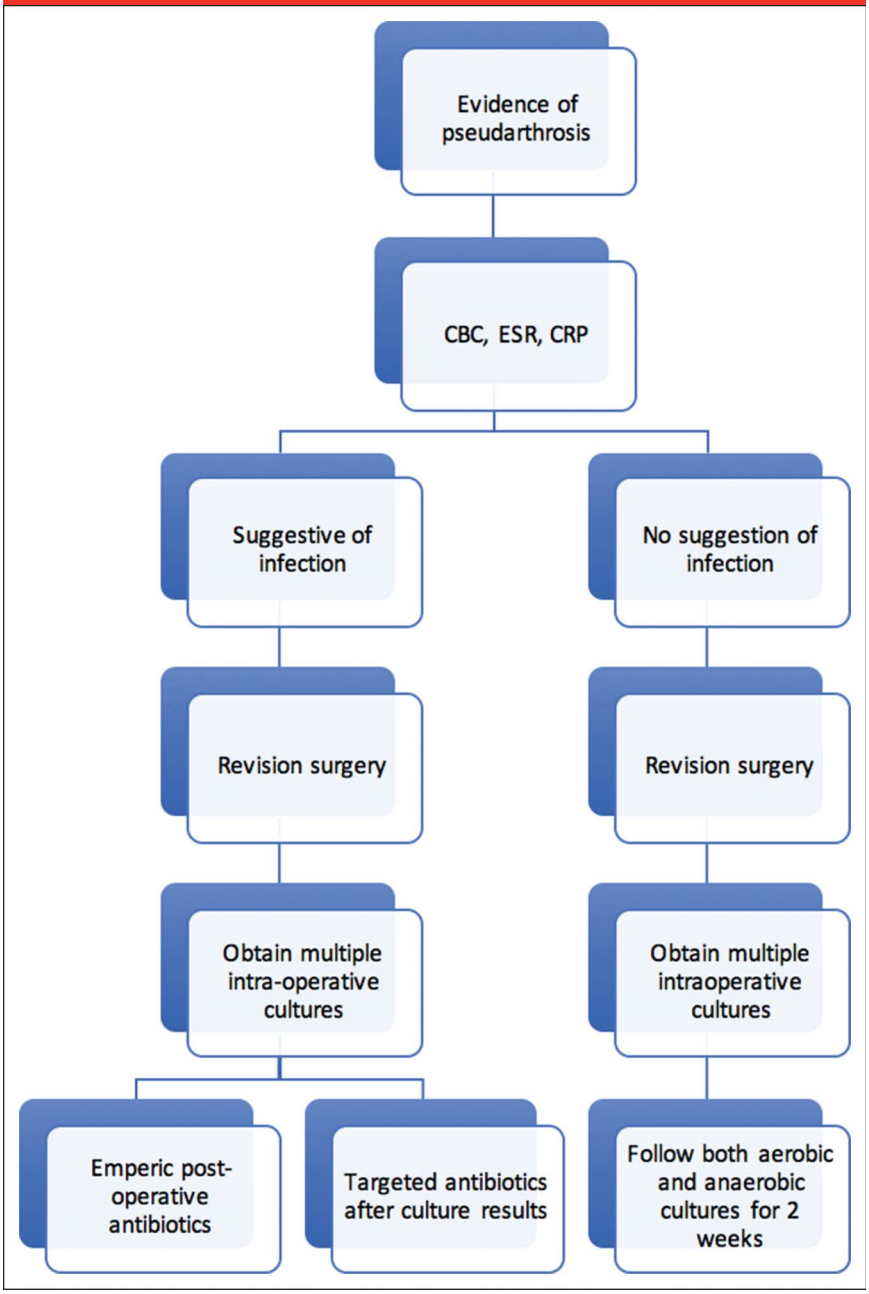
No clear consensus on treatment exists. Patients should be treated with parenteral antibiotics for at least 6 weeks, with some reports recommending 10 to 12 weeks.[11] Parenteral beta-lactam is typically the antibiotic of choice, unless it is a penicillin-resistant strain of *C acnes*.[6,11] Lifelong suppression antibiotics should be considered in patients who are unable to tolerate surgical intervention, or in those who fail more than one revision surgery with appropriate antibiotic therapy. Close follow-up is needed to ensure that patients do not have loss of deformity correction. Unlike non–implant-associated infections, outcomes of implant-associated infections secondary to *C acnes* are generally poor compared with infection secondary to other organisms.[18] Patients who are being treated for deformity may experience less correction compared with their noninfected counterparts.[19]

"Aseptic" Pseudarthrosis

The cause of pseudarthrosis after spine surgery is often related to patient factors (tobacco use, diabetes, and others), surgical technique (inadequate graft placement or poor fusion bed preparation), or mechanical factor (hardware failure, inadequate stabilization). Cases of symptomatic pseudarthrosis that warrant revision surgery should undergo an infectious workup with complete blood counts, ESR, and CRP because deep infection can result in pseudarthrosis. In cases where infection is not suspected clinically or has been ruled out with laboratory tests, the diagnosis of "aseptic pseudarthrosis" is made, with the assumption that a patient or technical factor is likely responsible. However, because of its low virulence and often indolent presentation, *C acnes* has been proposed as a possible causative agent in some presumed aseptic cases, considering that the ongoing infection may suppress local osteogenesis.

Shifflett et al[20] conducted a retrospective review of 578 revision surgeries performed for presumed aseptic pseudarthrosis and found that pseudarthrosis was the most common diagnosis for which intraoperative cultures were obtained (49.1%). In addition, pseudarthrosis was the most common reason in which intraoperative cultures were unexpectedly positive (55.6%). *C acnes* was cultured in 54.2% of patients with the primary diagnosis of aseptic pseudarthrosis. Given the high rate of positive cultures in these cases, some authors recommend that cultures

Figure 1



Workup and management of pseudarthrosis. CBC = complete blood count.

should be routinely taken and followed for an adequate amount of time to rule out *C acnes* infection, on revision surgery performed for pseudarthrosis.[20] Cases of pseudarthrosis complicated with *C acnes* infection can be considered as aseptic pseudarthrosis at the time of surgical intervention and treated with antibiotics postoperatively if cultures grow positive. Our suggested approach for the treatment of pseudarthrosis is outlined in Figure 1.

Degenerative Disk Disease

Although the exact pathophysiology of disk degeneration is poorly understood, it has been classically thought of as a premature onset of age-related changes in the intervertebral disk, including decreased water content, altered enzyme activity, and decreased end plate permeability.[21] Many etiologies, including genetic, biomechanical, traumatic, and vascular etiologies, have been proposed.[21] These are most likely the predominant mechanisms of degeneration of the intervertebral disk. However, until recently, the role of potential infectious mediators in the development of disk degeneration had not been considered. Some authors have speculated that the role of *C acnes* is analogous to that of *Helicobacter pylori* in peptic ulcer disease.[22] Although there is no clear evidence to support this dramatic link, the role of *C acnes* in degenerative disk disease is an expanding area of interest in the literature.

Modic Changes

Modic changes refer to MRI findings in the end plates adjacent to degenerative disks.[23] They were first described by Modic and can be either type 1 or type 2 changes. Type 1 changes refer to decreased signal intensity on T1-weighted images and increased signal intensity on T2-weighted images in the end plates and vertebral bodies adjacent to the degenerative disk. Type 2 changes refer to increased signal intensity on T1-weighted images and isointense or slightly increased signal intensity in T2-weighted images.[23] The most likely pathophysiology related to these changes is end plate fissuring and breakdown created by disk degeneration, and associated reactive inflammation and edema.[23]

Some controversy exists in relation to Modic type 1 changes. These changes are consistent with edema, can sometimes have a very similar appearance to spondylodiscitis, and thus may be secondary to infection by a low-virulent

organism, such as *C acnes*. In general, 4.2% of patients with type 1 Modic changes, but without other overt signs of infection, may develop pyogenic spondylodiscitis at 2 years of follow-up.[24] In addition, patients with low back pain and Modic type 1 changes have evidence of systemic inflammation that is not present or present to a lower degree in patients without Modic change or Modic 2 changes, respectively.[25]

Dudli et al[26] investigated the biologic plausibility of the ability of *C acnes* to cause type 1 Modic changes in a rat model. *C acnes* from a symptomatic human L4-5 disk with evidence of Modic 1 changes on MRI was isolated and inoculated into rat tail disks. This was found to lead to an upregulation of IL-1 and IL-6 within 3 days. Evidence of Modic 1 changes was observed at 2 weeks postinoculation. Chen et al[27] examined the effect of disk inoculation with *C acnes* compared with *S. aureus* species in a rabbit model and found that *C acnes* inoculation resulted in only moderate disk degeneration and Modic 1 changes on MRI, compared with more classic MRI findings of pyogenic spondylodiscitis seen with *S. aureus* inoculation. Shan et al[28] examined the effects of *C acnes* inoculation in lumbar disks in a rabbit model and found that *C Acnes* can survive within the end plate region of the intervertebral disk and cause an inflammatory reaction similar to Modic 1 changes on MRI.

Clinical studies have shown mixed results regarding a correlation between Modic 1 findings on MRI and the presence bacteria. Albert et al[29] found a relationship between anaerobic bacteria isolated in herniated disk material in patients undergoing lumbar diskectomy and new Modic type 1 changes. They asserted that disk herniations may provide opportunity for low-virulence organisms to enter the disk space and subsequently cause the phenomenon of Modic type 1 changes. Aghazadeh et al conducted a prospective study of 120 patients who underwent lumbar diskectomy, analyzing excised disk material for *C acnes* using polymerase chain reaction (PCR) to detect the 16S recombinant DNA (rDNA) specific for *C acnes*, first used by Fritzell et al.[30,31] They found that most patients with positive *C acnes* findings had evidence of Modic 1 changes on their MRI. In contrast, Wedderkopp et al[32] obtained vertebral body biopsies in 24 patients with evidence of Modic 1 changes on MRI and found that none of their cultures grew *C acnes*. Arndt et al and Rigal et al also did not find evidence to support a connection between *C acnes* and Modic 1 changes.[33,34] At this point, although *C acnes* provides an interesting etiology for Modic 1 changes, the connection between this MRI finding and indolent infection is not absolutely clear.

Disk Herniation

Stirling et al[35] were among the first to describe a potential relationship between low-virulent organisms, chronic infection, and degenerative conditions of the spine. They cultured disk material from 36 patients undergoing lumbar microdiskectomy and found that 19 patients (53%) had positive cultures after long-term incubation, of which 16 (84% of positive cultures) grew *C acnes*. Since the publication of their findings, the role of low-virulent organisms, most often *C acnes*, has remained a point of contention, with studies reporting conflicting results.

Several clinical and preclinical studies have supported the notion that *C acnes* may be an instigator in the development of degenerative disk pathology. Arndt et al[33] conducted a prospective study culturing the disks of 83 patients undergoing or were to undergo lumbar disk replacement. They found that 40 of 83 patients had a positive culture, including 18 patients with positive *C acnes* cultures. They admit that although intraoperative contamination is a potential explanation for their findings, as they did not have a contaminant control in their study, inflammation caused by these organisms may play a role in the initiation of the degenerative cascade. Agarwal et al reviewed a case series of 52 immunocompetent patients undergoing single-level lumbar diskectomy and found that disk cultures were positive in 19.2% of patients (n = 10), of whom 7 patients had positive *C acnes* culture. Zhou et al[36] conducted a study of 46 patients undergoing lumbar diskectomy. They used PCR to detect *C acnes*–specific 16S rDNA and muscle biopsy as controls and found that 23.9% of disk PCRs had positive findings for *C acnes*. In addition, *C acnes* was more likely to be found in disk herniations with an annular tear compared with those without an annular tear. Rao et al[37] reported a similar rate of 19.6% positive cultures from 168 patients who underwent anterior cervical, anterior lumbar, posterior cervical, or posterior lumbar spine. Although their findings confirm previous reports, Rao et al did not report a specific contaminant control.

Evidence incriminating *C acnes* in the degenerative cascade was also found at preclinical and translational levels. Chen et al[27] examined the effect of disk inoculation with *C acnes* compared with *S. aureus* species in a rabbit model and found that although *S. aureus* was associated with septic discitis as expected with high-virulent organisms, *C acnes* inoculation resulted in moderate disk degeneration and end plate rupture. Rajasekaran et al[22] performed a proteomic and 16S rDNA analyses of disk tissues obtained from 22 patients undergoing lumbar spine surgery. Using a combination of liquid chromatography-tandem mass spectrometry for protein analysis and PCR for 16S rDNA analysis, they found evidence of not only bacteria-specific rDNA but also host pathogen–specific proteins

evident of low-grade infection. Li et al[38] suggested that although the intervertebral disk is a suitable environment for *C acnes* growth, however, it is doubtful for *C acnes* to be able to inoculate the disk by means of bacteremia.

Other authors have refuted these findings and the role of *C acnes* and other low-virulent organisms in the development of degenerative disk disease. Carricajo et al[39] conducted a prospective study in 54 patients undergoing surgery for lumbar disk herniation to evaluate the presence of *C acnes* in degenerative disks. Along with obtaining cultures from the disks, Carricajo et al obtained control samples from surrounding ligamentum flavum and muscle, air samples, and laminar flow control samples. They found positive disk cultures in only 2 of 54 patients, in whom control samples from surrounding ligamentum flavum and muscle was also positive. They also found positive samples in control ligamentum and muscle samples, air samples, and laminar flow samples in patients who did not have positive disk samples; they strongly suggested that positive findings in other reports may be because of contaminants. Rigal et al[34] reported a 1.6% (n = 6) positive culture rate in 313 patients who underwent video-assisted anterior lumbar interbody fusion or anterior lumbar disk replacement; no cases of delayed or secondary infection was reported. Unlike the posterior approach, Rigal et al were able to obtain biopsy samples without any skin contact; they suggested that the anterior laparoscopic approach allowed a relatively low contamination rate.

Antibiotics in the Treatment of Low Back Pain

The possibility of a connection between infection secondary to low-virulent organisms and degenerative conditions of spine opens the door to the potential of treatment with antibiotics for chronic low back pain.[40] Albert et al[41] hypothesized that chronic low back pain and type 1 Modic changes on MRI after a previous disk herniation is related to a low-virulent organism infection.[40,41] They conducted a double-blinded, randomized, controlled trial in 162 patients with persistent back pain and type 1 Modic changes after a previous disk herniation comparing the efficacy of 100 days of antibiotics (ie, amoxicillin-clavulanate) against placebo. They found that patients in the antibiotic group did significantly better than those in the placebo for all primary and secondary outcome measures. The publication of these findings was met with significant controversy, with some authors pointing out critical issues with researcher conflicts of interest and certain aspects of study methodology and data analysis.[42,43] To our knowledge, no other study has been able to replicate the findings of Albert and colleagues, nor have antibiotics been tried as a primary treatment modality in patients other than the narrow subset of those with new Modic 1 changes after a previous disk herniation. We do not routinely use antibiotics in this patient population at our institution.

Limitations

One significant limitation in the findings by many of the studies reporting positive *C acnes* cultures in patients with degenerative disk disease is the inherent potential for contamination while obtaining cultures. Some studies have attempted to circumvent this limitation by focusing on proteomic analyses rather than strict culture results.[22] In addition, there has been a lack of standardization of obtaining cultures in many studies attempting to link disk herniation and *C acnes* infection. At this point, we suggest that although some studies provide a compelling case for a contributory role of *C acnes* in some degenerative processes of the spine, there is insufficient evidence currently to change our current understanding of the predominant pathophysiology or management of degenerative disk disease. However, unlike the degenerative spine setting, we do think that in patients with previous spine surgery, indolent infection should be on the clinician's differential.

Conclusion

The role of *C acnes* has grown from a nonvirulent organism that is part of skin flora to a potential major player in spine pathology, incriminated in native and implant-related infections, as well as to disk degeneration. Given its indolent clinical picture, diagnosis of infection secondary to *C acnes* can be difficult. *C acnes* in nonimplant or native spondylodiscitis is a rare infection that can often be missed or underdiagnosed. It is generally associated with previous spine procedures or surgery. Often, it has good outcomes with appropriate treatment. Postoperative *C acnes* infection in the setting of spinal hardware is also an indolent process that may not have the usual systemic or laboratory signs of infection; it may present many years after the index procedure. The treating surgeon should have a high index of suspicion for *C acnes* infection in the setting of sudden worsening of back pain after a long symptom-free period, because it is the most common cause of infection more than 1 year after the index procedure. In addition, there may be a role for cultures during surgery for aseptic pseudarthrosis because some of these cases may be related to *C acnes* infection. Most controversial is the role of *C acnes* in the degenerative processes of the spine. Conflicting results and controversy

regarding the role of *C acnes* in disk herniation, Modic 1 changes on MRI, and the role of antibiotics in the treatment of low back pain has stimulated more research in the area.

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