REVIEW ARTICLE

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Do bacteria play an important role in the pathogenesis of low back pain?

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Key words
displacement/microbiology, intervertebral disc, low back pain/etiology, review.

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Accepted for publication 7 December 2014.

doi: 10.1111/ans.12983

Abstract

Considerable interest has been generated recently regarding an alternative hypothesis for the pathogenesis of low back pain and radiculopathy in the presence of intervertebral disc prolapse. Traditionally, back pain and radicular (sciatic) symptoms have been attributed to mechanical compression of neural tissue by herniated disc material and to inflammation caused by exposure of the nerve roots to disc tissue. Recent research however has suggested that low-grade infection within the intervertebral disc by anaerobic bacteria may be responsible. The development of Modic changes in the corresponding adjacent vertebral endplates has also been suggested as an indicator of infection. This article is a thorough review of the current literature regarding the hypothesis that low-grade anaerobic bacterial infection may be the cause of disabling low back pain and radiculopathy.

Introduction

Low back pain (LBP) is a common complaint in the adult population causing an enormous economic burden to individuals and communities. Despite advances in the knowledge of spinal pathology, the estimated worldwide burden of back pain has risen from 58.2 million disability-adjusted life years in 1990 to 83.0 million disability-adjusted life years in 2010.[1] Often, the reported symptoms are not matched by imaging of the spine,[2] frustrating clinicians and patients alike.

Radicular pain due to herniated nucleus pulposus (HNP) is in part caused by mechanical compression of the nerve root. In addition, exposure of the nerve root to the contents of the nucleus pulposus has also been implicated in the pathogenesis of radicular pain by way of a chemical inflammatory radiculitis.[3–7] To treat this chemical radiculitis, early randomized trials of monoclonal antibodies to tumour necrosis factor (TNF) and interleukin-6 have been conducted. Results of these trials show promise as alternatives to epidural steroid injections for radiculopathy[8,9] by targeting the specific inflammatory mediators involved.

An alternative hypothesis, that infection with low-virulence organisms such as *Propionibacterium acnes* (*P. acnes*) may cause persistent LBP and radiculopathy in the presence of HNP[10] has generated considerable interest and comment in recent times. In 2001, Stirling *et al*.[11] first reported findings suggestive of chronic low-grade infection of the intervertebral disc causing an inflammatory response, irritating the nerve roots and resulting in persistent radiculopathy. Albert *et al*.[7] proposed a similar hypothesis, but suggested that the presence of vertebral endplate signal changes, also known as Modic changes (MCs), in the vertebral endplate may be an indicator of such low-grade infection. They argue that despite the avascularity of the healthy intervertebral disc, neovasculrization of the herniated disc allows seeding of bacteria in the disc during episodes of transient bacteraemia. Recently, this hypothesis has been tested through a pilot study[12] and a randomized controlled trial[13] of the treatment of chronic LBP by oral antibiotics, with positive results.

Several other studies have examined intervertebral disc material to test the bacterial infection hypothesis. The predominant organism identified is *P. acnes*, but several other organisms including coagulase-negative Staphylococci (CoNS), *Staphylococcus aureus*, *Corynebacterium propinquum*, *Citrobacter freundii* and *Bacillus cereus* have been identified. Some authors have suggested that growth of these organisms represents contamination of open surgical wounds, rather than true infection within the disc.[14–17]

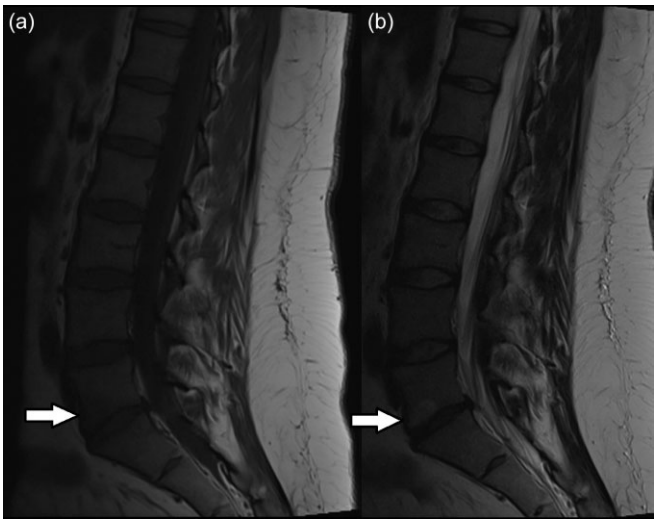

Fig. 1. Type 1 Modic changes; arrow points to lower endplate L5. Hypointensity on T1 weighted image (a), hyperintensity on T2 weighted image (b).

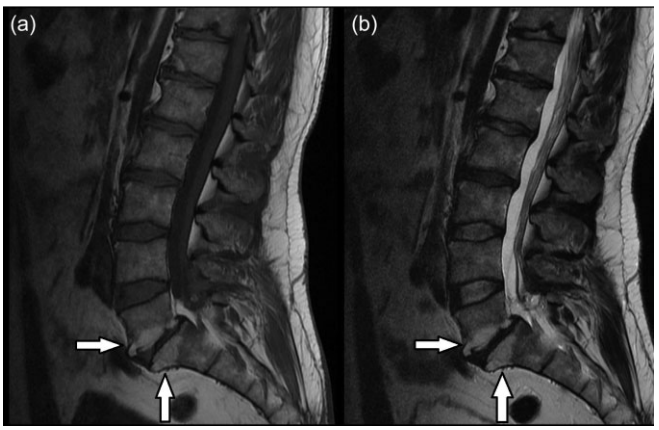

Fig. 2. Type 2 Modic changes; arrows point to lower endplate L5 and upper endplate S1. Hyperintensity on both T1 (a) and T2 (b) weighted images.

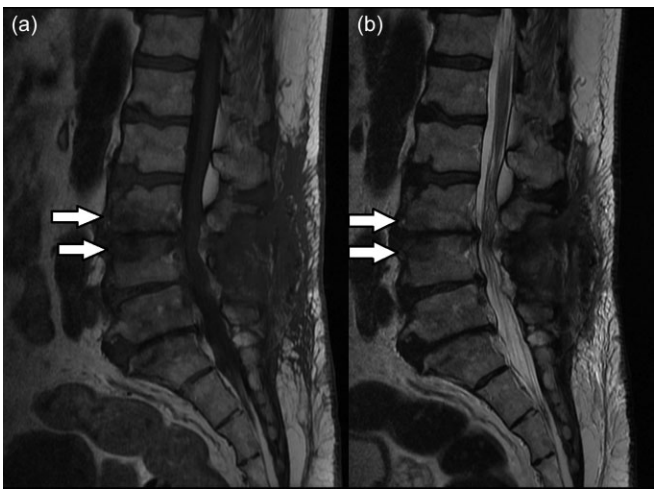

Fig. 3. Type 3 Modic changes; arrows point to lower endplate L3 and upper endplate L4. Hypointensity on both T1 (a) and T2 (b) weighted images.

MCs were first described in 1988[18,19] and are thought to represent a progressive degenerative pathology from inflammation to sclerosis. Numerous studies since have examined associations between the presence of MCs and various clinical and epidemiological indicators;[7,20–31] however, approximately 6% of the asymptomatic population may have MCs on magnetic resonance imaging (MRI), despite not reporting any back pain symptoms.[23]

Histopathological and immunofluorescence examination of intervertebral discs has shown a large number of macrophages,[32] interleukin-1 beta-immunoreactive cells,[32] TNF-immunoreactive cells[33] and protein gene product 9.5-immunoreactive nerve fibres[33] in herniated discs, compared with minimal evidence of inflammation in normal control discs.[32]

This article aims to review current research on the possible role of low-grade anaerobic bacterial infection of the intervertebral disc in chronic LBP, as well as the significance of MCs.

Literature review

Vertebral endplate signal changes (MCs)

Vertebral endplate signal changes were first described by Modic in 1988 and are grouped into three types.[18,19] Type 1 changes appear on MRI as hypointense regions on T1 weighted views, and hyperintense on T2 (Fig. 1). Type 2 changes, however, appear as hyperintense on T1 weighted views, and either isointense or slightly hyperintense on T2 (Fig. 2). Type 3 changes appear as regions of hypointensity on both T1 and T2 weighted views (Fig. 3), and on plain radiography are seen as bony sclerosis. In Modic's original study, 16 patients were followed up between 1 and 3 years later. It was noted that five of six patients with type 1 changes had progressed to type 2, while imaging in all 10 of those with type 2 changes remained stable. The histopathology of these regions was examined by Modic in small numbers as part of the initial description, finding disruption and fissuring of endplates with vascularized fibrous tissue in three samples of type 1 changes, while three samples of type 2 changes showed yellow marrow infiltration.

Few studies have subsequently examined the vertebral endplate microscopically since Modic's original description. A strong association has been reported between the presence of MCs and both TNF-immunoreactive cells and protein gene product 9.5-immunoreactive nerve fibres in a series of patients undergoing surgery for HNP.[33] The presence of such cells is consistent with inflammation and nerve ingrowth into endplates, and may help to explain the aetiology of persistent LBP. A recent study of the morphological characteristics of MCs found type 1 changes to feature higher bone formation and erosion ratios when compared with type 2 changes.[34] Type 3 changes were also found to have high formation and erosion ratios, reduced resorption and thicker trabeculae.

A greater number of studies have examined the clinical picture associated with MCs. The coexistence of both degenerative disc disease (DDD) and MCs at corresponding endplates has been shown

to be more distinct from those with DDD alone, than DDD is from patients with back pain and no discernible pathology on MRI.[21] This would suggest that the presence of both DDD and MCs together should be considered a distinct diagnosis, possibly requiring a distinct treatment approach. A systematic review of 77 papers conducted in 2008[23] featuring 82 study samples found that MCs were present in 6% of the asymptomatic population and 12% of the general population, compared with 43% in individuals with LBP. Other factors associated with MCs identified in the literature include presence of disc pathology and herniation,[22,26] increasing age[23] and anaerobic bacterial growth from intervertebral disc tissue.[10] A Finnish twin cohort study showed that MCs are typically paired, that is, occurring at both endplates corresponding to a single intervertebral disc.[30]

Low-grade bacterial infection of the intervertebral disc: systematic review

Methods

The PubMed database was searched for peer-reviewed articles that sampled intervertebral disc for the purpose of bacterial identification. Papers containing the MeSH terms 'intervertebral disc/microbiology' or 'intervertebral disc displacement/microbiology' were collected, finding 105 papers in total. Abstracts of all English language papers that studied humans were reviewed. Exclusion criteria included non-primary research, research on the topic of acute septic discitis or vertebral osteomyelitis and absence of intervertebral disc culture or polymerase chain reaction (PCR; Fig. 4). A total of eight papers were included in the meta-analysis (Table 1).

Data regarding specimen collection methodology, culture technique, perioperative antibiotic usage and culture results was collected for analysis (Table 1).

Results

Bacteriology of intervertebral discs. A total of 404 patients across eight papers were studied (Table 1). Three-hundred and ninety-four specimens were sent for bacterial culture and identification, and PCR for identification of bacterial DNA was performed on 71.

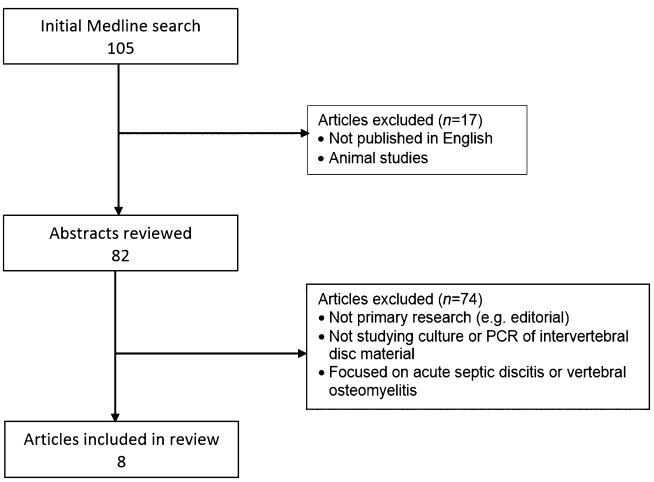

Fig. 4. Literature review summary of excluded papers.

A total of 132 (32.7%) patients were found to have bacteria in the intervertebral disc; however, the yield varied widely between papers (6.7–48.2%). The most frequently detected organism was *P. acnes* (68.9%), followed by CoNS (22.0%). One study performed only PCR analysis on specimens from 10 patients, finding *B. cereus* in one, and *C. freundii* in another.[37] Only one study[10] performed both PCR and culture on specimens, and found that both techniques produced identical results. The PCR sequence used in this study was specific for the detection of *P. acnes*.

Culture techniques and incubation times differed between authors. A combination of agar and broth enrichment media was used but culture results from specific techniques were typically not reported. Incubation times varied from five to 21 days in total. An incubation time of 7 days or longer was associated with higher yield ($P = 0.0263$) although only one study incubated culture media for less than 7 days. The ideal incubation time to optimize yield of *P. acnes* while minimizing growth of contaminants has been studied in relation to prosthetic joint infection diagnosis. An incubation time in this circumstance of at least 13 days is thought to be necessary for adequate yield.[39] Prosthetic joint infections due to *P. acnes* are also typically low grade and subacute or chronic but this suggested incubation time does not necessarily apply equally to the culture of intervertebral disc.

The spinal procedure performed was predominantly microdiscectomy for symptomatic HNP (76.0%); however, one study[35] examined a cohort of patients with DDD undergoing total lumbar disc replacement but no mention of coexisting HNP was made. This series found a 48.2% rate of bacterial growth, predominantly *P. acnes* and CoNS. Thirty patients in a series reported by Ben-Galim *et al.*[16] underwent microdiscectomy for HNP, however 12 patients also had an additional procedure such as transforaminal lumbar interbody fusion. Stirling *et al.*,[11] the first group to report on bacterial growth from disc material, also took disc specimens from 14 control subjects undergoing spinal procedures not related to HNP. Of these control subjects, none grew bacteria, in contrast with a growth rate of 52.8% in patients undergoing microdiscectomy. Excluding those patients undergoing surgery for indications other than symptomatic HNP, bacterial growth was reported in 26.8% of patients across all papers.

A study by Wedderkopp *et al.*[14] examined biopsies of vertebral body endplates rather than discs, in a series of 24 patients with Modic type 1 changes on MRI. Biopsies were obtained percutaneously under fluoroscopic guidance. Samples from two patients were positive, one growing *S. epidermidis*, and one CoNS. Both patients were treated with oral antibiotics for 3 months although both results were considered contaminants. No sustained symptomatic improvements were recorded in either patient.

Albert *et al.*[10] performed bacterial culture and PCR on 61 immunocompetent patients undergoing single level lumbar disc surgery for HNP. No patients in their series had a history of prior spinal surgery or epidural steroid injection. Bacterial organisms were cultured in specimens from 28 (45.9%) of 61 patients. Twenty-four of 28 (85.7%) patients grew *P. acnes*, and two (7.1%) grew CoNS.

Albert *et al.*'s bacterial culture results were also compared with MRI findings preoperatively and at 1–2 years post-operatively. They

Table 1 Details of papers included in review

Author	*n*	Bacteria identified	*P. acnes*	CoNS	Antibiotics†	Method
Albert[10]	61	28 (45.9%)	24 (85.7%)	2 (7.1%)	N	Culture, PCR
Arndt[35]	83	40 (48.2%)	18 (45.0%)	16 (40.0%)	Y	Culture
Agarwal[36]	52	10 (19.2%)	7 (70.0%)	1 (10.0%)	Y	Culture
Carricajo[15]	54	4 (7.4%)	2 (50.0%)	1 (25.0%)	N‡	Culture
Ben-Galim[16]	30	2 (6.7%)	0	2 (100%)	Y	Culture
Fritzell[37]	10	2 (20.0%)	0	0	N	PCR
Stirling[11]	50	19 (38.0%)	16 (84.2%)	2 (10.5%)	?	Culture
Rollason[38]	64	27 (42.2%)	24 (88.9%)	5 (18.5%)	N	Culture
Total	404	132/404 (32.7%)	91/132 (68.9%)	29/132 (22.0%)	166/354 (46.9%)	

†Prophylactic antibiotics given prior to collection of disc specimen. ‡One patient in this series received prophylactic antibiotics, their culture result was unknown. CoNS, coagulase-negative Staphylococci; PCR, polymerase chain reaction.

found that 80% of patients with a positive anaerobic culture had developed new MCs at the site of disc herniation, compared with 44.1% of patients who were culture-negative ($P = 0.0038$). Neither of the two patients with aerobic growth only developed new MCs. Prevalence of MCs on preoperative MRI was not reported; however, Arndt *et al*.[35] reported no statistically significant correlation between culture results and MCs on preoperative MRIs in their study of lumbar disc replacements.

In another paper, Albert *et al*.[13] published a randomized controlled trial of oral antibiotic treatment against placebo for persisting LBP of at least 6 months in duration, with known HNP and Modic type 1 changes on MRI. The study population did not discriminate between patients who had undergone surgery or on the distinction between back and leg pain. They found statistically significant improvements in the treatment group for Roland Morris Disability Questionnaire and EQ-5D scores, as well as several pain and disability-related scales, where the placebo group showed minimal improvement.

Several studies have been at odds with Albert *et al*.'s work. McLorinan *et al*.[17] investigated the likelihood of contamination of specimens taken during 79 open spinal procedures by taking samples of skin, wound tissue, and a saline washing of the wound. Culture and immunofluorescence microscopy were used to identify organisms. Bacteria were identified in 29.1% of skin samples, 21.5% of wound tissue and 16.5% of washings. The predominant organism identified from all sites was *P. acnes*, followed by CoNS. Bacteria identified on immunofluorescence microscopy typically appeared as single cells, rather than large aggregates, which is more consistent with contamination than infection.

Several attempts have been made to investigate and minimize the possibility of contamination of disc material from the skin, air in the operating theatre and during the processing of tissue specimens. Ben-Galim *et al*.[16] developed a methodology for sampling disc tissue with as little contamination as possible, stating that 'a meticulously sterile surgical technique was used to perform surgery'. Dissection and plating of specimens was performed in the surgical field immediately by the surgeon to minimize exposure of the tissue to contamination. No growth of *P. acnes* was found in this group and two patients grew CoNS. In addition to intervertebral disc samples, Carricajo *et al*.[15] took muscle and ligamentum flavum biopsies, air samples in the operating theatre both prior to and during surgery, and cultured a control plate exposed to 30 s of laminar air flow while specimens were plated in the same cabinet. They found 7.4% positive growth in discs, of which half were *P. acnes* but 22.2% positive growth in muscle or ligamentum flavum samples, all for *P. acnes*. All positive disc cultures also had positive muscle or ligamentum flavum cultures. 7.4% of laminar flow controls were culture positive, predominantly for *P. acnes*. Operating theatre air sampling taken on four occasions did not find growth prior to the start of the surgical list but samples taken during operations contained a mixture of *P. acnes* and CoNS.

Few studies have compared bacterial culture of the disc with histopathological features. Arndt *et al*.[35] found that multinucleated cells were observed in 33% of discs with positive cultures, compared with 5% of discs with negative cultures ($P = 0.038$). Another study[40] found a strong association between herniated intervertebral discs and both presence and number of inflammatory cells in inner and outer annulus fibrosis samples ($P < 0.001$), compared with degenerated discs that were not herniated. This study however did not examine bacterial infection of disc material.

Antibiotic prophylaxis. In our review of studies involving bacterial culture of disc specimens summarized in Table 1, perioperative antibiotic usage appeared variable among authors. In three papers, prophylactic antibiotics were administered to all patients prior to specimen collection; in four papers, antibiotic prophylaxis was withheld until specimens were collected (except in one patient in Carricajo's study,[15] where antibiotics were given); and one paper did not comment on antibiotic usage. It was not possible to ascertain whether the one patient in Carricajo's study who received antibiotics prior to specimen collection subsequently had a positive culture or not. This prevented precise analysis of pooled data, and results are reported as a range to include all possible outcomes. Between 31.3% and 31.9% of patients who received antibiotics prior to specimen collection had a positive culture, compared with 31.9–32.5% in whom antibiotics were held. A Fisher's exact test found no significant correlation between administration of antibiotics prior to specimen collection and yield of bacterial growth ($P = 0.9–1.0$) across all patients. On exclusion of a study in which patients did not undergo surgery for HNP[35] and of another in which only PCR on disc specimens was performed[37] (Table 2), statistically significantly fewer patients who received antibiotics subsequently grew bacteria (14.5–15.6% versus 32.6–33.1%, $P = 0.0016–0.0044$).

Table 2 Effect of antibiotic administration prior to specimen collection

	Positive culture	Negative culture
Antibiotics given	12–13 (14.5–15.7%)	70–71
Antibiotics held	58–59 (32.6–33.1%)	119–120

Summary of results in papers where bacterial culture performed, antibiotic usage reported and indication for surgery was herniated nucleus pulposus ($P = 0.0016–0.0044$). Culture status of one patient given antibiotics unknown; therefore, precise results not available.

Antibiotic levels in the normally avascular disc have been studied, with varying results. Gibson *et al*.[41] found no detectable levels of flucloxacillin or cephadrine in the discs of adolescents undergoing scoliosis surgery and in an animal model Fraser *et al*.[42] found very low levels of cephazolin in the disc 30 min after administration, becoming undetectable at 60 min. More recently, several studies[43–46] have found measureable levels of cephalosporins in the majority of discs although not necessarily in concentrations above the minimum inhibitory concentration to prevent *S. aureus* growth. It has been argued that the internal structure of the disc plays an important role in its permeability. A degenerated or herniated disc would be expected to have a higher antibiotic concentration than that sampled from a younger and more normal disc, such as that encountered in paediatric scoliosis surgery.[46,47] Gentamicin has been shown to have superior penetration of discs when compared with cefuroxime, with detectable levels in 100% and 20% respectively, despite adequate serum concentrations.[48] This is consistent with an *in vitro* study,[49] which proposed that the electrical charge of the antibiotic may also play a role, stating that positively charged aminoglycosides would cross the negatively charged glycosaminoglycans of the disc more readily than negatively charged penicillins or cephalosporins.

Discussion

Low-grade anaerobic bacterial infection of the intervertebral disc is a hypothesis that has challenged the status quo of the pathogenesis and treatment of lumbar disc herniation. Evidence exists both in support and against this concept but results are difficult to interpret as the bacteria in question are of low virulence and historically have been considered skin contaminants in surgical tissue specimens. Low-virulence bacteria such as *P. acnes* and CoNS are increasingly becoming appreciated as a cause of delayed prosthetic joint infections and implant loosening, and the distinction between clinically insignificant contamination and true infection is the focus of ongoing research.[50,51]

Ben-Galim *et al*.[16] were unable to prevent the growth of CoNS despite meticulous attention to sterility during collection of disc tissue and immediate dissection and plating of specimens intraoperatively. Of note, however, they did not find any growth of *P. acnes* and a low rate of growth overall when compared with other studies. Carricajo *et al*.[15] and McLorinan *et al*.[17] reported significant levels of bacterial contamination from control samples including muscle, ligamentum flavum, wound washings and skin as well as laminar air flow cabinets and operating theatre air samples. The nature of these low-virulence skin commensal organisms makes the challenge of distinction between infection and contamination a difficult one. Albert *et al*.[10,12,13] have reported not only a significant rate of bacterial infection in herniated discs but also strong evidence of symptomatic improvement after antibiotic treatment in patients who had previously failed an extended period of conservative treatment.

Evidence for the adverse effect of exposure of the nerve roots to nucleus pulposus material is well documented.[3–6] Therefore, the presence of inflammatory cells in the annulus fibrosis of herniated discs[35,40] does not necessarily support the infection hypothesis. A strong association between inflammatory cells in discs with positive bacterial culture has been reported[35] but actual numbers were small, and it is difficult to draw any firm conclusions. It is also possible that both infectious and chemical inflammatory processes may be occurring simultaneously.

Administration of routine prophylactic antibiotics, where reported, resulted in a statistically significant reduction in yield of bacterial growth across all papers that sampled herniated intervertebral discs. It is typically understood that antibiotic administration prior to specimen collection reduces yield of bacterial culture; however, the same is not necessarily true of PCR techniques, which rely only on the presence of bacterial DNA rather than the ability to grow. Further comparative studies are required to confirm this. The evidence for cephalosporin penetration into intervertebral disc suggests that it is variable and that the window in which adequate concentration is achieved for antimicrobial prophylaxis is narrow.[42,44] This narrow therapeutic window means that growth may not be significantly inhibited even if cephalosporin antibiotics are administered, depending on the time elapsed between dosing and specimen collection.

If the disc infection hypothesis were to gain adequate supporting evidence, the next challenge would be to define a therapeutic approach. For example, antibiotic resistance is a major developing problem around the world and, if used inappropriately, the proposed 100-day course of oral amoxycillin/clavulanic acid has the potential to greatly influence this increasing level of resistance further. Therefore, sufficiently accurate diagnostic tools would be needed to prevent patients complaining of back pain associated with lumbar disc herniation from unnecessarily protracted courses of antibiotics prior to considering surgery. Albert *et al*. reported an association between anaerobic bacterial infection of the intervertebral disc and development of Modic type 1 or 2 changes at 12 months post-surgery; however, their paper does not report the prevalence of MCs at baseline, nor the length of time between pain onset and surgery. The development of MCs at 12 months does not assist in the formulation of a treatment plan for the patient presenting with new onset sciatic pain associated with HNP. A statistically significant relationship between growth of anaerobic bacteria and subsequent development of MCs was reported; however, a 44% false-positive rate is unacceptably high to the treating clinician. More specific predictive factors and factors that could be used at the time of diagnosis are needed before a protracted oral antibiotic regime could be considered for use beyond the research field.

The radiological appearance of MCs is well defined. Their role in LBP however is still unclear. In a paper by Kjaer *et al*.,[21] the combination of DDD and corresponding MCs was proposed as a distinct group from both DDD alone and non-specific LBP without obvious radiological changes, but no suggestion was made of change in their

management. MCs are found in asymptomatic individuals, even though they occur far more frequently in clinical populations and in association with other pathology, most notably disc degeneration. Although inflammatory cells and nerve ingrowth are frequently found in endplates with MCs, the core pathology that causes this process is still unclear. Mechanical injury of the endplate in the presence of disc degeneration is one possible cause.

Conclusion

Promising results in support of the disc infection hypothesis have been published, but it is obviously too early to drastically alter one's practice. The greatest challenge in this field of research is the distinction between true disc infection and contamination of specimens. Future studies of the microbiology of the disc should increasingly focus on this distinction. This could be achieved by further attempts at minimization of contamination during specimen collection and correlation between identification of bacteria and presence of other markers of infection (such as inflammatory cells or elevated blood inflammatory markers). Additionally, establishment of criteria (such as those used for the diagnosis of prosthetic joint infection) to distinguish between infection and contamination would greatly assist future research efforts. Further independent studies are required to validate the use of oral antibiotics in clinical practice and diagnostic tools with greater utility in predicting those who may respond are needed to prevent treatment of a large number of patients inappropriately, with the potential for substantial side effects. Although definitive evidence is lacking, the disc infection hypothesis has the potential to cause a paradigm shift in the approach to back pain caused by HNP and as such should not be dismissed lightly.

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