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Should We Start Treating Chronic Low Back Pain with Antibiotics Rather than with Pain Medications?

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For those of us who have read the 2 recently published articles by a Danish – British research group, it might appear that we are observing an impending paradigm shift on the origins of chronic low back pain. The results of this research indicate, that chronic low back pain associated with bone marrow edema in vertebral endplates that are adjacent to herniated intervertebral discs may be caused by infections with anaerobic bacteria of low virulence. According to these articles, treatment with certain antibiotics is significantly more effective than placebo against this low back pain. If these findings are to hold true in repeat studies by other researchers, they stand to fundamentally change our concepts of low back pain, degenerative disc disease and in consequence the suitable therapies for these entities. It may in fact require pain specialists to become familiarized with the details of antibiotic treatments and their specific risks in order to be able to properly counsel their patients. While this seems hard to believe at first glance, bacteria have been implicated in the pathogenesis of other conditions that do not primarily impose as infectious diseases such as gastric ulcers. While the authors refer to a few previous studies pointing into the same direction, the relevant research is really only from one group of collaborating scientists. Therefore, before we start prescribing antibiotics for chronic low back pain, it is imperative that other researchers in different institutions confirm these results. (Korean J Pain 2013; 26: 327-335)

Key Words:
antibiotics, discitis, low back pain, Modic changes, Propionibacterium acnes.

INTRODUCTION

It is only a few months, since a research group from Denmark and the United Kingdom proposed an association between infections of herniated discs caused by *Propionibacterium acnes* (*PA*), chronic low back pain (CLBP) and bone marrow edema in the adjacent vertebral endplates [1]. In a parallel publication, they reported on the successful treatment of this condition with antibiotics as compared to placebo [2]. These 2 publications were accompanied by introductory remarks from the journal's editor-in-chief [3]. The press and the scientific world have responded with high interest – print and online media are ripe with promises about a new cure for CLBP and specialty clinics for such treatments have opened up. The journal, which published these two controversial manuscripts, has received

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numerous critical letters to the editor. He deemed it necessary to discuss these letters and the author's responses together in yet another editorial [4-12]. While the strengths and problems of these 2 publications will be discussed in some details later on in this review, it is obvious that in our current time with immediate and unlimited media propagation, the repercussions of such findings could be enormous. It is impossible to keep the necessary discussion within the scientific arena and this carries a significant risk with regards to the side effects and complications (both, for individuals and for public health) of long-term antibiotic treatments that may be initiated without the secured diagnosis of a spinal infection. We may also ask, what the novelty behind the idea of *PA* infections of intervertebral discs really is. After all, the concept that spinal infections can be caused by anaerobic pathogens is not new and while a large review on the topic of anaerobic osteomyelitis was published in 1978 [13], the first report on a spinal infection caused by *PA* originates from 1975 [14] and the first report of postoperative discitis with this pervasive anaerobic germ was published already in 1987 [15]. The following review will attempt to put these recent publications and the enormous attention they have received into a wider perspective and to make a cautious assessment as to where further research might take us and what this may imply for our treatment of patients with CLBP.

SUMMARY OF THE 2 STUDIES

1. Does nuclear tissue infected with bacteria following disc herniations lead to Modic changes in the adjacent vertebrae? [1]

In this study, the authors investigated a prospective cohort of 67 patients (67 at inclusion − 61 at final follow-up) undergoing primary disc surgery at a spinal center in Southern Denmark. All the study subjects had a magnetic resonance imaging (MRI) study performed at baseline and at between 1 and 2 years of follow-up. The disc herniations were required to have penetrated the posterior annulus. During surgery and under meticulously sterile conditions, 5 biopsies of nucleus material were separately obtained in each case and immediately frozen at −80°C in individual glass vials, only then were the perioperative antibiotics (1.5 g cefuroxime intravenously) administered. There were 3 cases were intraoperatively, according to the manuscript, no nucleus material could be obtained. All specimens were processed at a specialized laboratory in the United Kingdom and cultured on aerobic and anaerobic media. Gram staining was performed and cultures identified to be *PA* were further investigated by means of polymerase chain reaction (PCR) for 16S rDNA with specific primers. The preoperative and the follow-up MRI studies were interpreted by a blinded consultant radiologist and graded for the presence and the degree of bone marrow edema (Modic type 1 changes [16]) in the vertebral endplates adjacent to the operated disc. The investigators found positive bacterial cultures in 46% of cases and anaerobic growth in 43% of cases. In case of positive cultures, 86% were positive for *PA* and all of these were confirmed by PCR, whereas all negative cultures were also negative in PCR testing. Out of 25 patients with a positive anaerobic culture, 20 (80%) developed new Modic type 1 changes between the preoperative MRI and the follow-up MRI, whereas only 5 did not. In contrast, out of 34 patients with a negative culture (and PCR), only 15 (44%) developed new Modic type 1 changes between the preoperative and the follow-up MRI, whereas 19 did not. None of the 2 patients with purely aerobic growth developed new Modic changes. From these data, the authors derived a statistically highly significant association between herniated discs that had anaerobic contamination/infection prior to surgery and the development of new Modic type 1 changes during the follow-up period. The investigators interpreted these results as proof of their own findings in an earlier study and of previous findings by other investigators. They hypothesized, that *PA* may be spreading from foci in the body, predominantly the skin or the oral cavity, on a regular basis and that during bacteremia these microbes may reach and survive in body areas of low oxygen tension and with no or minimal vascularity. Supposedly, in the blood stream and in well-oxygenized tissues these obligate anaerobes are not able to survive and multiply. This, according to the authors could explain why persons in whom this anaerobic bacteremia takes place do not fall ill. A degenerative nucleus would − according to this theory − be colonized with *PA* via the neovascularization that often occurs at the location of an annulus defect, when reparative granulation tissue is being formed. Because of the absence of blood vessels inside the nucleus and the anaerobic environment especially inside a degenerative nucleus, *PA* can survive inside it. The bone marrow edema in the adjacent endplates that is represented by Modic type 1 changes in MRI would then be the

inflammatory reaction of the vertebrae to an infected nucleus.

2. Antibiotic treatment in patients with chronic low back pain and vertebral bone edema (Modic type 1 changes): a double-blind randomized clinical controlled trial of efficacy [2]

In this study, after screening 347 patients with lumbar disc herniations in MRI, 162 participants with lumbar pain, a disc herniation and new Modic type 1 changes in the vertebral endplates adjacent to it were randomized into 4 groups: 2 with 45 patients each and 2 with 36 patients each. The first 2 groups received either single or double dose antibiotics (amoxicillin/clavulanic acid) for 100 days; the second 2 groups received either single or double dose placebo for 100 days. Outcome measures were the Roland Morris Disability Questionnaire, lumbar pain according to a specific rating scale, quality of life as measured by the EQ-5D score, MRI Modic grading and some other parameters. MRI studies were performed prior to treatment and at 1-year follow-up. There was a relatively high amount of side effects in the antibiotic group (65%), which were mainly gastrointestinal. The rate of such side effects in the placebo group was only 23%. The drop out rates were also significantly different with 13 in the antibiotic and only 5 in the placebo group. With an overall follow-up rate of only 89%, the investigators found a superior outcome with antibiotic therapy as opposed to placebo. This advantage was both statistically significant and clinically relevant (as judged by the minimal clinically relevant change). According to their assessment, the clinical improvement with antibiotic therapy was superior to any other currently established treatment. This clinical improvement was paralleled by a reduction in the volume of the Modic type 1 changes in the antibiotic group, whereas no such reduction was observed in the placebo group. The authors argued, that their antibiotic regimen was responsible for the observed improvement and interpreted this effect as well as the changes in the MRI studies as a direct result of the antibiotic treatment acting upon low-grade *PA* infections present in the treated discs and causing the low back pain as well as the bone marrow edema in the adjacent vertebral endplates. However, no confirmatory microbiological testing was performed in this second study. In conclusion, they stated that in a special subgroup of patients with CLBP and Modic type 1 endplate changes, antibiotic treatment could be an option after all other treatments have failed.

CRITICAL EVALUATION OF THE 2 STUDIES

The key message of these two studies really hinges on a logical connection being made between them. This logical connection is, that based on the results of study 1, it is assumed that also in study 2, colonization of the disc herniations with *PA* was the underlying pathology. It is then implied, that this colonization was the source of both, CLBP and Modic changes in the participants and that this pathology was successfully treated by the administration of antibiotics. While no formal microbiological testing was performed in study 2, which could have corroborated the link between the 2 studies, there is a very strong indicator, that this logical connection cannot be justifiably made: The percentage of women participants in study 1 was only 27% whereas in study 2 it was 58%. This alone is indicative of a severe selection bias and shows that the samples used in the two studies do not represent the same, normally distributed source population. Does the spine center in question predominantly operate on men or have more women than men refused to participate in this study? If so, based on which factors? But there are additional issues that put into question the logical basis for the conclusions reached by the authors.

With regards to study 1, the authors' argumentation consequently takes aim at CLBP as being connected with Modic type 1 endplate changes and with *PA*-colonization of discs. This specific group of investigators has published a number of previous papers that all point into the same direction [17-20]. But it is also understood, that CLBP probably is the least accepted indication for performing disc surgery and the authors give no details whatsoever on how these indications for disc surgery were made and whether there were other clinical symptoms that would have justified an operative intervention. It also remains unclear, which operative technique was used and whether the disc spaces were entered with instruments as opposed to simple sequestrectomies from the spinal canal. It has been shown, that manipulation within the disc space alone at the absence of infection may cause endplate changes [21]. It would also be interesting to learn, why no disc material could be obtained from 3 individuals intraoperatively when a confirmed disc herniation was one of the pre-

requisites for inclusion into this study. When looking at the creation of this cohort, no details are given as to how many persons were screened regarding study participation and based on what criteria selections were made. In view of the severe sex bias in the cohort, this information would be crucial before attempting to interpret the results.

Study 2 has many more critical issues than study 1. It also begins with the question of selection bias when recruiting the study participants. Potential candidates were recruited from two secondary spine centers, not the center leading the study and it is not explained why no patients were recruited from the leading center. The initial inclusion criteria were age between 18 and 65 years, MRI-confirmed disc herniation L3/L4 or L4/L5 or L5/S1 within the preceding 6 to 24 months and lower back pain of 6 months duration. The article mentions that patients were invited to participate and sent questionnaires and the study starts with 347 potential participants from which they eventually included 162. But we don't learn how the authors identified the potential candidates for receiving a questionnaire, how many questionnaires were sent out, what the return rate was and how many of the candidates that answered found entry into these 347 patients. The manuscript further states, that "patients also had to have low back pain in the area of L1 to L5 with a numerical rating scale score of $\geq$ 6". But there is no reflection of this additional criterion in the flow chart explaining the study flow. It is therefore possible, that patient recruitment was influenced again at a later stage. The power calculation to determine the required sample size was based on a 2-group study design (antibiotic versus placebo), but - supposedly because of a last minute intervention by the ethics committee - the design was altered to a 4-group design in order to allow for an examination of different antibiotic dosages. So in fact, 4 different groups were studied, even though the manuscript states that the dosage comparison was not formally tested. Despite this precautionary statement by the authors, this makes the study design a 4-group-comparison and the study was almost certainly underpowered. As a consequence, existing differences might have been missed or remained not statistically significant. It remains completely unclear from the manuscript, how a credible randomization strategy could have resulted in one group (antibiotics, 45 single dose + 45 double dose) with 90 patients and another group (placebo, 36 single dose + 36 double dose) with 72 patients. The use of a computer-generated randomization list with such large numbers of patients should have come much closer to a 80 versus 82 distribution. The study included surgical and conservative patients, but no details are given on their relative proportion and on the relative distribution of surgical and conservative patients between the groups. This again could be the basis for a bias between the groups. At outset, there was a statistically significant difference between the groups with regards to the presence of only minimal (with regards to volume) Modic type 1 endplate changes (10.4% in the placebo group vs. 28.8% in the antibiotic group). The authors argue, that the presence of only minimal edema should predispose to a more favorable outcome, which would make the observed improvement in the antibiotic group even more impressive in comparison to the placebo group. The opposite, however, is the case: As long as we accept the concept, that the bone marrow edema in the vertebral endplates correlates with the inflammatory process and with the pain caused by such a process, patients with a lot of edema stand to benefit much more from a treatment targeting the edema-causing process than patients with hardly any edema. So in fact, the two groups were biased towards greater potential benefit in the antibiotic group. At least a relevant part of the observed effect could potentially be attributed to the effect of anti-inflammatory medication, including potential anti-inflammatory side effects of the antibiotic (even if small) as well as to the natural course. The publication further states that "patients were allowed to take their usual anti-inflammatory and pain relieving medication". No details are given on what these were and whether there was a difference between the groups. So in summary, there are a number of reasons to suspect serious problems with confounding factors. No details are given on whether some patients had received epidural steroid injections prior to study inclusion. The rate of visits to a general practitioner or a specialist during the 1-year study period was twice as high (41.8%) in the placebo group than in the antibiotic group (23.4%) without any additional details being given. It would have been important to know what treatments were prescribed to these patients by these physicians or what additional medications they received. The study focuses on a potential inflammatory or infectious process. Interestingly enough, neither C-reactive protein (CRP) nor interleukin-6 (Il-6) nor a sedimentation rate were part of the laboratory investigations. While these parameters are

not typically elevated in CLBP [22], they should have been a logical component of the laboratory setup when an infectious agent is expected to be involved. At 1-year follow-up, 13 patients were lost in the antibiotic group (14%) and only 5 (7%) in the placebo group. It is conceivable that depending on how the outcomes of these missing participants would have been, the study results could have been very different ones, especially in view of the above-mentioned problems with statistical power.

So in summary, these two studies, which have generated an enormous media response, are far from convincing with regards to their central message. This does not abrogate the fact that the authors may be onto something extremely interesting and that in fact a paradigm shift may be on the horizon. It does however mean, that based on these data alone, there is no sufficient justification to start treating CLBP with Modic type 1 endplate changes adjacent to disk herniations with antibiotics, unless an infection is confirmed by biopsy.

THE RELEVANCE OF *PROPIONIBACTERIUM ACNES* (*PA*) WITH REGARDS TO SKELETAL INFECTIOUS AND INFLAMMATORY CONDITIONS

The interest in *PA* and to a lesser extent in other anaerobic pathogens reaches back quite a long time. As mentioned earlier in this review, *PA* has been implicated in osteitis and osteomyelitis as a sole or as a concomitant pathogen as early as the 1970s [13-15,23]. It is not absolutely clear from some of those early descriptions, in how far they might have described conditions that we nowadays might put into the context of SAPHO syndrome, a complex inflammatory disease with immunological components in its pathophysiology. This syndrome derives its acronym from the key symptoms synovitis, acne, pustulosis, hyperostosis and osteitis and was first described in 1972 [24]. A very similar syndrome that predominantly affects young persons and that shares some of the same features (namely palmar pustulosis and affection of the spine) was first described as chronic recurring multifocal osteomyelits (CRMO) in 1978 and has been under intense investigation ever since [25]. The distinction of these 2 syndromes has been difficult and there still is no consensus as to how connected they are and as to their precise pathophysiology. But with both entities, *PA* has been found in biopsies of the affected bones [26-36]. The presence of *PA* also ties in well with the palmar pustulosis, a skin pathology. Other anaerobic pathogens have also been implicated in some of these papers, but especially with the reclassification of a number of anaerobic germs, it is difficult to precisely compare the causative agents in older publications with those reported in more recent ones [37]. There is increasing evidence, however, that with these specific syndromes, *PA* may play a pivotal role. It is still unclear, what exactly the pathogenetic process is and how much of it is related to host factors [38] and how much to a low-virulence, ubiquitous skin and oral germ. The current consensus sees these syndromes as a combination of an infectious condition, autoimmune processes and genetic predisposition [26,28,29,31]. The idea of an immunologic-inflammatory process rather than an overt infection would also make sense in view of Stirling's work, that has implemented *PA* in sciatica [39], a condition that often has a clear inflammatory component and where proinflammatory cytokines from degenerative nuclei are thought to play an important role.

Beyond the aspect of autoimmune conditions affecting the skin and the skeleton, *PA* is a very relevant problem germ in implant infections. Here also, the course of such a contamination can be very much like a low-grade infection in some cases, but very inflammatory and clinically symptomatic in other cases. It is speculation, but the host-specific immune response to *PA* may vary quite widely between individuals. *PA* typically resides in the oral cavity and in the deeper layers of the skin, especially in the hair follicles and in glandular structures. This makes it more difficult to be killed off by surgical skin preparations [40] and hence increases the risk of a potential surgical site contamination during longer procedures or simply from the deeper skin layers exposed at the incision edge. Especially in the context of instrumented spinal surgery, high rates of surgical site and implant contaminations with *PA* have been reported and in many cases with an extremely delayed time course (the longest reported delay being 23 years), again suggesting the relevance of host-related immunological factors in controlling a pathogen of normally low virulence [27,41-61]. The low virulence of *PA* and possibly in dependence of the specific immune system of a given host may also be responsible for a lacking laboratory response to a progressive infection, as has been reported in some cases [43].

One additional complicating factor when trying to assess studies that examine microbial contamination in disc material as well as on the surface of implants is that anaerobic germs like *PA* are difficult to culture and are much easier missed than other, especially aerobic bacteria, such as staphylococci. This is especially true when the colony counts are low and when perioperative antibiotics are being used. Anaerobic cultures often need to be incubated for extended periods of time in order to turn positive and depending on the laboratory setting, these plates might often be discarded before they ever had a chance to yield a positive result. Once, they turn positive, there is also the possibility that they may be dismissed as "skin contaminants" by the processing laboratories, since *PA* is typical for the skin flora. Albert et al. have argued in the same direction when discussing other studies that did not find positive cultures when sampling disc material from surgeries [62]. Overall, it is more likely than not, that the actual presence of *PA* in chronically herniated discs and on the surface of spinal implants is currently still underappreciated [63].

If we are ready to accept, that colonization or infection with *PA* may be a more relevant problem than generally accepted, we are faced with the question of how best to combat this anaerobic bacterium. The authors of the 2 studies discussed above decided on amoxicillin/clavulanic acid for a period of 100 days. They based their choice of antimicrobial agent on the consensus advice of 3 independent expert microbiologists. In other studies where *PA* infections or *PA*-associated syndromes such as CRMO and SAPHO were treated, penicillin, macrolide antibiotics such as roxithromycin and azithromycin, clindamycin, the tetracyclin doxycyclin as well as recently daptomycin have been used with success [32,35,64,65]. In some cases, however, disease relapse was noted after discontinuation of the antibiotic therapy [32]. One study looking at the in vitro susceptibility of anaerobic bacteria found metronidazole to be the most effective antibiotic against *PA*. The capacity of *PA* to form biofilms, especially on implant surfaces, makes this microbe much less accessible for many antibiotics and daptomycin may be a more effective choice than other antimicrobial agents because of its biofilm-penetrating capabilities [64]. This however entails the risk, that a reserve antibiotic may in the near future become overused in an uncontrolled fashion for the therapy of CLBP, a frightening idea. Ongoing efforts to create a vaccine against *PA* could in the future become an alternative option for treating these complex infections and PA-associated syndromes [66].

DISCUSSION AND CONCLUSIONS

So should we start treating chronic low back pain with antibiotics rather than with pain medications? Based on the analysis presented above and on the currently available evidence, the answer to this question is a clear "No". Granted, there are strong hints towards an infectious or immunologic process that may be responsible for CLBP in a specific subgroup of patients. The two papers discussed here are only the most recent and at the same time the best research so far with this possible pathophysiology in focus. But given the various problems that have been highlighted above, these two publications alone cannot serve as a justification for long-term antibiotic treatments in low back pain sufferers with bone marrow edema in the vertebral endplates adjacent to a disc herniation. If an infectious pathology is suspected, a percutaneous biopsy with culturing for aerobes and anaerobes as well as a PCR analysis for bacterial DNA needs to be the diagnostic standard at this point in time. The risks of such a diagnostic procedure are low. In experience hands, under imaging guidance and under local anesthesia, it can be performed safely, effectively and with little patient discomfort. This balances well against the risks of several months of antibiotics, both for the individual and for public health. Hardly any innovation in our field justifies to sacrifice the core standards of good clinical practice and the principle that diagnosis comes before treatment whenever possible is one of them. While we need to be conservative when translating these new findings into clinical practice, we should be very ambitious in confirming them or demonstrating them to be incorrect. Professional societies that focus on spinal diseases and low back pain need to establish or advance their existing registries so that biopsy materials from disc surgeries can be investigated on a larger scale and across institutions. Laboratory procedures need to be standardized between the various institutions so that culturing can be performed in a way to reduce the risk of missing anaerobic low-grade infections. Governments and non-profit organizations need to fund research in high-volume institutions in order to duplicate the results of Albert et al. Only after these are confirmed by other re-

searchers, should we begin to act on their findings in terms of new therapies. And we should be prepared for surprise results by such research: There is a recent study, which suggests that disc degeneration may be caused by viral infections [67]. Disc degeneration by means of viruses, chronic low back pain and Modic changes by means of anaerobic bacteria?

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