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LETTER TO THE EDITOR

Antibiotics for low back pain?

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Dear Editor,

Recently, two articles published in *European Spine Journal* have caused some interest [1, 2]. Their message is that anaerobic bacteria (AB) may enter degenerated discs, for example because AB circulate abundantly in the blood stream when people brush their teeth, resulting in a slow-acting infection, the secondary effect of which is inflammatory processes in the adjacent vertebral bodies. These are visible on MRI and called "Modic changes" (MC). It has previously been shown that MC may be painful, and hence an entirely new illness model is proposed to explain low back pain (LBP) in a certain proportion of patients. Contrary to most other models, this one comes with an effective treatment, comprising 100 days of antibiotics without having identified a pathogen.

In the first article [1], the authors claim to have shown that AB are found quite frequently in degenerated discs and that patients with such bacteria more commonly develop new MC than others. In the second article [2] they report on, what they describe as, a double blind randomized controlled clinical trial of efficacy, comparing antibiotic treatment against placebo in patients with chronic LBP and MC. They conclude that the treatment is more effective than placebo in all outcomes.

With the implications of such findings, considerable media interest has inevitably been generated including a press conference held in London at which some of the authors participated. During this event, a British neurosurgeon is quoted as having said that the main investigator, the physiotherapist Hanne Albert, deserved the Nobel Prize. However, it transpires that this same neurosurgeon is in fact involved in a business venture in a company, Mastmedical.com, together with at least two of the major authors (Hanne Albert first author and Claus Manniche, head of the research department at that time). This company appears to have been dormant for several years, perhaps waiting the unveiling in London. These two authors, in addition to their full-time positions at the Spine Center in Middelfart, Denmark, have additional private clinics devoted to the treatment of MC. Hanne Albert has for some years been involved with a private clinic together with a pediatrician advertising itself as a clinic specializing in the treatment of MC using antibiotics and laser treatment (Modicklinikken.dk says in danish: "we can cure back pain"). Claus Manniche recently started his own similar clinic (www. Modicspecialisten.dk). Treatment in these clinics is not cheap and is largely not reimbursed by social insurance. These financial interests were not reported under "competing interests" in the two published articles, which has evoked some cause for concern, and has certainly made me read them with great care. As a result I have the following questions and comments:

In the first article [1] the authors investigate: (1) whether AB would be present in degenerated discs removed surgically and (2) If MC would have developed 1–2 years later at the level of the infected disc.

They found such infected discs to be present in almost half of the study participants (usually infected by the acne bacterium) and that new MC were more likely to develop in people with such infected discs than in those without. In other words, 57 % of people with new MC would have had an acne-bacterium infected disc vs. 44 % of those without new MC. I find the study confusing for four main reasons:

1. Inclusion in the study was open to people with or without MC, and the presence of bacteria was studied at baseline. One year later, the development of new

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MC was studied and linked with the presence of bacteria at baseline. However, the researchers missed out on the opportunity to study the association between bacteria and MC at baseline. As the bacteria would have been present at that time, MC could have already developed, and so it would not be necessary to wait for a year in order to see if there was a link between infected discs and MC. An analysis of this association also at baseline would have strengthened the study. In fact, the prospective study design does not guarantee causality between the bacterial presence at baseline and the follow-up presence of MC, as study participants were included whether or not they had MC.

2. Did they study MC type 1 or type 2? In the method section it is clearly stated that "At the follow-up MRI the occurrence of new MCs type 1 or type 2 at the level of the previous disc herniation was graded as a positive finding". However, in the Discussion the authors state that "the findings of this study could be interpreted as a support to the theory that the occurrence of MCs type 1 in the vertebrae adjacent to the previously herniated disc might the oedema surrounding an infected disc". In the Conclusion of the Abstract, it is also said that this study is about MC type 1. It would be helpful if the authors could clarify which type they did study. Was it MC type 1 (presumably the actively inflamed stage) or type 2 (the presumed reparatory stage)?
3. The hypothesis appears to be that AB are the only bacteria capable of living in the anaerobic disc. Why then were there also aerobic bacteria in the discal material? My conclusion is that they would be there as a result of contamination. The authors explain and discuss in detail how they attempted to prevent contamination from the skin, obviously because they were looking for the acne bacterium, frequently found on the skin and in subcutaneous hair follicles. But antiseptic fluids would hardly penetrate into the subcutaneous tissue. Furthermore, as this bacterium is apparently also present inside the body, contamination could conceivably come from the body fluids. How would it be possible to extrude disc material under sterile conditions avoiding contact with subcutaneous tissue and body fluids?
4. I presume that there would be two major approaches to determine the presence of pathogens in bones. One of these is well documented and has been used for decades [3, 4]. According to this method, five samples should be collected from each specimen. One or two positives out of these findings would be indicative of contamination, whereas three or more would be considered a significant growth. The other approach would be to take one sample per person. What puzzles me is why the research team collected five disc tissue samples from each patient, but only report on the findings in relation to the number of patients who had a positive culture. If five samples were taken, I would have expected a report of how many of these were positive, and how many individuals had at least three positive findings out of the five possible.

   Obviously, if some of the positive cases reported here arise from <3 positive samples, the estimated prevalence of "infected" discs would have to be adjusted. I encourage the authors to provide clarification on these issues.

   As regards the second article [2], I also have some questions that I hope that the authors will be able to help me with.
5. "Both conservative and surgically treated patients were included". How many of them had undergone surgical treatment one or more times, and how were they distributed between groups? Bacterial contamination might have occurred during an operation.

   The initial inclusion criterion regarding age was 18–65 years. Yet in the flow chart (Fig. 1), after random allocation into groups, two patients are excluded with the explanation that they were more than 65 years. Why would the authors include people until the age of 65 to later exclude them as they grow older? Either they should not have been included in the first place because at some point during the study they would reach 65 or they should have been left in because they fulfilled the inclusion criteria at baseline.

   MC type 2 has not been listed as an exclusion criterion anywhere. Nevertheless, according to the flow chart (Fig. 1) one person was excluded because of "Modic 2". It seems to me that as with the two older patients, this one person with MC type 2 (all from the treatment group) should not have been excluded from the study/analysis. Further, three patients with new disc herniation were also excluded from the analyses in both groups, but there does not appear to be an explanation as to why?
6. The study design is somewhat perplexing. According to the Government Clinical Trial Registry, where this study was registered prior to commencement, the researchers intended to study two strengths of antibiotics. This is apparent in the flow chart, which has four potential arms; single dose antibiotics matched with single dose placebo and double dose antibiotics matched with double dose placebo. An equal number of patients is found in both antibiotics groups ($n = 45$) and in the placebo groups ($n = 36$).

The type of randomization method to obtain these equal numbers was not mentioned. Thereafter the two antibiotics arms were grouped together into one as were the two placebo groups. Why were the analyses not performed independently for the two sets of data? Under "Sample size" the last sentence can be read: "to fulfill a late request from the Danish Medical authorities a dose-response part was included, but the study is not designed for this tertiary purpose and therefore this is not formally tested." It is unclear what this request could be. Which Danish medical authority could have been involved in the analytic stage of this work, thus interfering with the researchers' right to select their study design?

7. Whether blinding of the clinical assessor was obtained or not is unclear. In the method section the text reads: "the patients and the observer were blinded to the allocation and all previous measurements. All physical examinations were performed by the same blinded observer". How could the observer (one of the authors?) be blinded to previous measurements at follow-up when having performed all physical examinations at base-line?
   In relation to the patients, antibiotics tablets have a strong and characteristic odour as has the urine of treated patients. This problem has not been discussed, and I could find no report of how well the blinding had worked out at the end of the study.
   The study is entitled "double-blind", but it seems to me that this may not in fact be the case.
8. The statistical analysis was described as having been performed by an independent professor in statistics, who is not identified as an author or under acknowledgements. Communication may be difficult when the statistician is not part of the research team.
   On reading Table 3, it became apparent that the data were not normally distributed, as average values were generally reported as medians and upper/lower quartiles. However, two of the estimates were supposedly normally distributed as they were presented as means with standard deviations (SD). But curiously, for "days with sick leave last year", the SDs are much larger than the mean values in all four cases where this variable is reported, thereby indicating that the data were not normally distributed. For example 18.9 days of sick leave has a SD of 61. Perhaps this can be explained by a typing error, with a decimal point having been omitted from the SD? But even more peculiar is the second mean value, namely that of "General improvement in %", stated to be 39 % in the treated group with a SD of 38.4 vs. 1.8 % in the control group with a SD of 31.7. No missing decimal point can account for those results, which clearly tell us that the estimates have a very high degree of variation. It would be interesting to know how this was dealt with in the analyses, and to see how the distribution looks with a mean of 1.8 and a SD of approximately 30!
9. At a first glance, the difference between groups is impressive, but a closer look plunged me into confusion. Table 3 describes the outcome variables at baseline, at 100 days follow-up and at the 1-year follow-up, showing average values of continuous data. For the first time, I have now witnessed a group of patients with LBP studied more than once over a period of time, remaining perfectly stable. This is apparent in the placebo group for several variables. The back pain variable with possible values from 0 to 10 had a median value of 6.3 both at baseline, after 100 days, and again after 1 year. The EQD had a median value of 60 (possible range 1–100) at all three times. A further three of the variables twice appeared to be identical (both at 100 days and after 1 year). It is very unusual for data to remain so stable in a fluctuating disorder such as LBP. Perhaps the analyses should be undertaken once more by an independent person, to ensure that there are no serious misunderstandings.
10. Is it likely that antibiotic treatment can eradicate AB? The trial comparing treatment with placebo included patients with LBP and MC type 1. However, patients were included without having obtained a positive bacterial culture, and after treatment it was not known whether any bacteria had disappeared.
    A curious finding is the fact that the total number of MC (reported as small and moderate/large) according to Table 4 remained unchanged in the treatment group after 1 year but diminished somewhat in the placebo group (142 and 142 vs. 130 and 120). The authors point out that patients in the treatment group have more MC moving from moderate/large to small volume, but they fail to take into account that of the MC reported in Table 4, 24 % were small to start with in the placebo group vs. only 11 % in the treatment group. It may be easier to become smaller when you start off large (regression towards the mean).
11. In the press and on some websites, it has already been noted that this study is unusual in that it does not have much of a placebo effect. Regression towards the mean is normally seen as a natural phenomenon and because people tend to seek treatment when they are in pain. Thus one would expect a tendency towards improvement also in the placebo group. In Table 4, the percentages of persons with various symptoms and findings are presented. These are shown as values at baseline and the 1-year follow-up for the two

groups. I calculated the size of differences in before-after estimates for the two groups and found them to be large, ranging between twice and 11 times larger improvements for the treatment group over the placebo group. The improvement is very small in the placebo group ranging from 6.9 % ("had low back pain in the past year") to 16.4 % ("had pain during springing test"). Nonetheless, although the outcomes were very good for the treatment group (there was a 55.8 % improvement on "had constant pain in the past year") nowhere could I find the 80 % cure as in the information that appears to have been divulged by some of the authors (youtube.com/watch?v=coPKgCLDsl). And as I had seen no rebuttal on this issue, I believed this to be the case until I read the original articles. When scrutinizing the percentages in Table 4, there are no such cure or improvement rates; 67.5 % in the treatment group still report LBP after 1 year, 20 % still have constant pain, and almost one-third of those treated with antibiotics have disturbed sleep at night due to pain.

12. Adverse events is an important issue when dealing with long-term antibiotics treatment. However, there is no description in the Methods section of when, how and by whom data on adverse events were collected. One could therefore suspect that perhaps this was during follow-up in an interview or as an open question in a questionnaire. Generally, the role of the various investigators in this study has not been explained and it would be reassuring to have this clarified. If the data were recorded in an unsystematic fashion, patients may not have known what adverse effects to look out for, and the reports would also have been difficult to classify afterwards. It would also be necessary to explain what is meant by "These were mainly low-grade gastroenterological complaints such as loose bowel movements, increased flatus or burping…" What happened to those who were not included under "mainly"? Also, I was surprised that there were no cases of dermatitis or vaginal thrush among the reported cases. In my experience, the latter is a common and annoying side-effect among women who are on even much shorter treatment programs with antibiotics.
13. It is mentioned that improvement took 6–8 weeks to manifest. However, as far as I can see, there were no points of data collection other than at baseline, after 100 days and 1 year, and there is no explanation in the Methods of how this information was obtained.
14. Finally, there are issues of considerable public health importance. (1) Treatment with antibiotics always carries the risk of the emergence of resistant bacteria. (2) Assuming that it is correct that the acne bacterium enters the blood stream en masse during teeth brushing or from the hair follicles, and assuming that these bacteria are able to enter the damaged disc to cause painful MC, and further assuming that antibiotic treatment can remove these bacteria thus curing MC-induced LBP, what happens next time the patient brushes his teeth and bacteria again enter the (still) degenerated disc or another one? Is he then back to another 100 days of antibiotics and if so, is this a viable solution to improve this type of back pain for whenever it occurs and recurs? In other words, is this a suitable treatment model from a public health perspective? If it is to be taken into common use, several high quality studies must agree on the results.

In sum, I ended up with many questions that I feel should be answered before it is possible to judge the full scientific value of these two articles. Most importantly, were the discs really infected? Was the clinical trial really blind? Why do the data look so peculiar? Is this model of disease and proposed treatment genuinely ground-breaking, or do the two articles merely serve as a justification for some of the authors' own clinical activities? Could they possibly even unintentionally have been influenced by financial interests?

Conflict of interest None.

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