Answer to the Letter to the Editor of Svend Lings entitled “Antibiotics for low back pain?” concerning “Antibiotic treatment in patients with chronic low back pain and vertebral bone edema (Modic type 1 changes): a double-blind randomized controlled trial of efficacy” by Albert HB et al., Eur Spine J (2013) 22:697–707

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Published online: 21 September 2013
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The author of this Letter to the Editor claims that he felt that he needed to review this paper carefully because Professor Claus Manniche, in addition to his full-time job, recently started a clinic where he treats patients with Modic changes and chronic lower back pain. It is not true that Claus Manniche after the publishing of the paper has established a private clinic, but in June 2013 he has started a position as being responsible for the research activity in a private clinic, which specializes in treating patients with Modic changes who are not able to receive treatment in the national health system. We feel that this is confirmation of the results of the trial and that he should be praised for providing this service. A professor would not participate in any clinic if the study was not scientifically extremely sound and provide a treatment where this specific group of patients does experience meaningful improvement with conventional care. If Professor Claus Manniche did not support this treatment that would be rather more suspicious.

An author of a Letter to the Editor has to obey same rules as authors of scientific papers. Postulations need to be proven. This letter is full of undocumented postulations. For example, SL states that on the website belonging to Modicklinikken.dk it says in Danish: “We can cure back pain...”). This is the first of many incorrect postulations, because this clinic only concerns itself with patients with Modic changes and only writes about them. Furthermore, this wording is simply not present.

Another faulty postulation is that SL claims that we write in our paper “*the authors claim to have shown that*

AB (anarobi bacteria) is found quite frequently in degenerated discs”. We do not claim any such thing. We have shown that bacteria have been found in extruded nucleus material in disc herniations. Disc degeneration is an extremely wide definition and we have not studied this.

SL claims that we investigated “*Whether AB would be present in degenerated discs removed surgically*”. We have not claimed any such thing. We investigated if any bacteria were present in the extruded herniated nucleus material. This is clearly stated in the title of the paper “Does nuclear tissue infected with bacteria following disc herniation lead to Modic changes in the adjacent vertebrae?”. Furthermore, it is not true that we only looked for AB (anaerobic bacteria). In Table 1 it is clearly marked that the analysis was carried out for both anaerobic and aerobic bacteria.

SL wonders why we did not study the association between a possible presence of bacteria at baseline and presence of Modic changes, and he thinks that we miss out on this opportunity. I presume that this stems from his previous misunderstanding where he thinks that we studied “*degenerated discs removed surgically*”. We only had permission from The Ethical Committee to remove the extruded herniated disc material, and this was also our only interest. Patients would naturally get rather upset if after a surgery for a lumbar disc herniation they were told that lumps of their disc were removed or worse as SL describes “*degenerated discs removed surgically*”.

SL’s conclusion is that the bacteria are present as a result of contamination. SL claims that “*Furthermore, as this bacterium is apparently also present inside the body, contamination could conceivably come from the body fluids*” and doubts that it would be possible to have surgery without contamination. Well, only 44 % had infected nuclear material so it is indeed possible to undergo surgery

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without contamination. During surgery all tissue were pulled away from the wound and great care was taken not to touch the side of incision. SL claims that the anaerobic bacteria are in what he call body fluids". Science shows that bacteria are not present in body fluids in general, but in the blood and only the first 10 min after tooth brushing as regards P Acne. When the macrophages identify the bacteria they devour them. I cannot imagine any surgery for lumbar disc herniation where the extraction of the nucleus material is taking place in less than 10 min after the patient had brushed their teeth. Therefore, his theory that contamination stems from body fluids is not true.

SL apparently thinks that we are searching for bacteria in the bone, "*I presume that there would be two major approaches to determine the presence of pathogens in bones*". This is not true; we were not searching for bacteria in the bone, but rather in herniated disc material. SL quotes the original 32-year-old paper from Kamme where 5 biopsies were taken. Many approaches to identify infection have been developed in the past 32 years, and this study is not the fountain of truth. We do have the information from the 5 biopsies, and the team evaluated that this information's was more appropriate in a coming detailed paper dealing with the details about the cultures, MIC, etc. This paper is in press [1]. So SL is welcome to look up the information when the paper is published.

SL writes that in the inclusion and exclusion: "*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*". This information is clearly stated in table 2 line 16. It is also stated that there were no significant differences between the numbers of previous surgeries in the two groups at baseline; therefore, this should not affect the difference between the groups.

SL questions: "*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*". This unfortunate situation is due to the fact that the investigating team thought that the time of inclusion was at the time of a positive MRI. At this time both patients were 64 years old. But in the waiting period before the examination and randomization these two patients turned 65. The Unit of Good Clinical Practice stated that inclusion was when they were randomized and given the tablets; therefore, they ruled out these two patients.

SL questions "*why a person with MC Type 2 was excluded*." This is due to the fact that this person only had MC type 2". Due to a secretarial error this person was

wrongly offered participation in the study, but at the inclusion examination the blinded examiner saw that the patient only had Modic type 2 changes and, therefore, did not fulfill the inclusion criteria. The GCP unit decided that the patient should be excluded and that we could not use the tablets for a new patient.

SL wonders why these previous three patients are not included. The answer is, that these patients did not fulfill the inclusion criteria and are, therefore, not included in the analysis.

SL "*notes that 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?*" Having an acute lumbar disc herniation is a very painful experience and we wanted to evaluate the effect of the treatment with Modic changes. Patients with other serious diseases such as cancer or being run over by a truck would contaminate results and so would patients with acute lumbar disc herniations. The number was three in each group and, therefore, it should not impact the results.

SL also finds the study design is somewhat perplexing concerning randomization. The randomization was performed by the Central Pharmacy, Odense University Hospital, using a computer-generated randomization list. This system is known and approved by the GCP unit of University of Southern Denmark. The study was originally designed as placebo versus antibiotic treatment, but in the late stages of planning The Danish Medical Authorities came with a "request" that they wanted a dose-response study included. We did fulfill their "request" but did not alter the number of participants.

SL writes that "*The study is entitled "double-blind", but it seems to me that this may not in fact be the case*". *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?*" Unfortunately, SL is apparently not aware of the definition of a blinded study. Being blinded means not knowing which treatment the patient receives. If the study is double blinded this means that both patient and examiner do not know which treatment the patient received. If we were to employ the new definition that SL suggests, i.e. that the examiner is not blinded because the examiner can remember which tests were positive 1 year ago at baseline, it is going to be difficult to carry out proper clinical trials! Furthermore, it would never be possible to blind the patients according to SL's definition because they would always know how they were at baseline. Patients probably know this much better than the examiner.

We have another postulation from SL, where he proposes that the antibiotic tablets result in a strong and characteristic urine odour in treated patients, and that this causes a problem with the blinding. Unfortunately, SL has

not studied the side effects properly, or he could have taken the trouble to read a patient information leaflet. Then he would know that Bioclavid does not give the urine a characteristic urine odour. Other antibiotics do, but not those used in our study.

SL worries because the statistics was performed by an independent statistician and expresses concern that “Communication may be difficult when the statistician is not part of the research team”. We found that we had excellent communication with the statistician, and furthermore think that we should be praised and not scolded for using an independent statistician who did all the calculations while blinded to the treatment groups.

SL claims that “*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*”. Firstly, SL uses the press and some unnamed websites as the source of a postulation that it is unusual that there is no placebo effect in the control group. Instead of these non-scientific sources it would have been more reliable if he had been able to find support for this claim in the scientific literature, which he is obviously unable to do. Many studies have been carried out on nonspecific CLBP, which is what the term indicates, non-specific, and there are in many of these studies a considerable placebo effect and little treatment effect. But in this study we have followed the recommendations of the European guidelines [2] and carried out research on a specific subgroup of CLPB patients; patients with Modic changes. If SL had studied the literature he would have found two other studies in addition to ours that included a control group and only treat patients with Modic changes. Chao et al. [3] evaluated the effect of various intradiscal injection regimens for patients with CLBP and Modic changes in a double-blind RCT with 120 patients where the control group was compared with diprosan and diprosan + songmeile and evaluated at 3 and 6 months. The control group did not have any improvement at any time, but the intradiscal injection of corticosteroids gave a short-term effect. The study by Jensen et al. [4] also studied 100 patients with Modic changes only, comparing exercise and staying active with rest periods in an RCT during a treatment period of 10 weeks. Follow-up was at 10 and 52 weeks. No relevant differences were observed between baseline and 52 weeks. These two treatments were ineffective to these patients and, therefore, the patients remained stable on all outcome measures, as was the case with our placebo group.

SL states that “*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*”. These patients were not recruited while they came to the two back centers as patients seeking care. They were

identified with a previous MRI-confirmed disc herniation L3/L4 or L4/L5 or L5/S1 within the preceding 6–24 months and between 18 and 65 years old. Individuals who fulfilled these criteria were posted a letter..... etc. They were identified via the MRI files and, therefore, you will not expect regression towards the mean.

SL suspects that data on adverse effects were collected in what he terms an unsystematic way “*that perhaps this was during follow-up in an interview or as an open question in a questionnaire*”. SL does not need to be suspicious about anything. This information was gathered according to the precise instructions of The Unit of Good Clinical Practice at the University of Southern Denmark. At baseline, all patients were given medical instructions as to how to take the drug, precautions as to how to avoid possible side effects, i.e. eating yogurt and other recommendations. Furthermore, all of the possible side effects that the medical company had on their leaflet of patient information were listed in the same order as the medical company had described them on the leaflet of patient information. In their informed consent the patients were instructed to report any serious side effects immediately according to the rules of GCP, and the team had to report any serious side effect to the Danish Medical Council immediately. Furthermore, at the 100-day follow-up patients were instructed to list all side effects they had experienced. Therefore, SL’s suspicion that the patients did not know which side effects to look out for is simply inaccurate.

We reported that “These were *mainly* low-grade gastroenterological complaints such as loose bowel movements, increased flatus or burping...”. Then SL “*was surprised that there were no cases of dermatitis or vaginal thrush among the reported cases*”. This inference is also incorrect. We did not write there were no instances of dermatitis or vaginal thrush; we wrote that the main complaint was low-grade gastroenterological complaints. We could have used many of our precious words listing every minor complaint including the patient in the placebo group who had 4 vaginal fungal infections confirmed by swabs by the gynecologists or the patient in the placebo group who suffered from constant vomiting to a degree that the vomit contained fresh blood towards the end of treatment. This degree of detail is not interesting for the reader, particularly with the limited amount of words permitted in a manuscript.

SL points out that “*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 one year, and there is no explanation in the Methods of how this information was obtained.*” At the 100-day follow-up, patients were instructed to write a brief patient history since we did not

know how this would be answered the question was open ended. The most common remark was that it took 6–8 weeks before they felt any improvement in pain.

Finally, SL worries about the public health importance. He worries that treatment with antibiotics always carries the risk of the emergence of resistant bacteria. We agree that we should all worry about multi-resistant bacteria. However, resistance occurs with partial treatment in contagious diseases, not in Modic changes where there is no contamination from other persons. Therefore, the worry can be minimal in this case.

He also has doubts that the bacteria enter the blood-stream during tooth brushing “*Assuming that it is correct that the acne bacterium enters the blood stream en masse during teeth brushing or from the hair follicles*”. We have never claimed that the bacteria enter the blood via the hair follicles. Many studies carried out by dentists have shown this and a few are listed in the paper [5, 6]. Then, if the patient is cured SL goes on to speculate “*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?” In our theory we state that we hypothesize that these anaerobic bacteria enter the disc as normal bacteremias as a result of the neovascularization-associated disc herniation. So, this is not an endless cure of antibiotic but the patients may be at risk the next time they experience a disc herniation, which fortunately is not all that frequent.

SL speculates that 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”? The accusations make us wonder what his motivation was for writing such a weak Letter to the Editor which is full of undocumented accusations, misunderstandings and demonstrates a poor understanding of the principles related to carrying out randomized controlled clinical trials?

Conflict of interest None.

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